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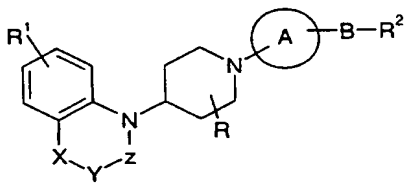
(54) Title: NEW P2X7 RECEPTOR ANTAGONISTS FOR USE IN THE TREATMENT OF INFLAMMATORY, IMMUNE OR CARDIOVASCULAR DISEASES



(I)

(57) Abstract: The invention provides piperidine compounds of general formula (I) in which A, B, X, Y, Z, R, R^1 and R^2 are as defined in the specification, their use as medicaments, compositions containing them and processes for their for their preparation.

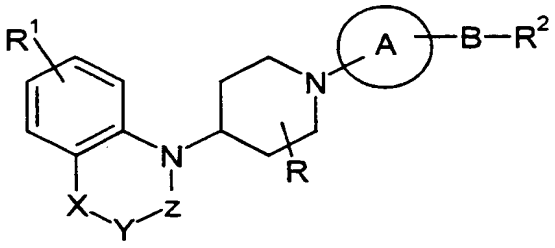
NEW $P2X_7$ RECEPTOR ANTAGONISTS FOR USE IN THE TREATMENT OF INFLAMMATORY, IMMUNE OR CARDIOVASCULAR DISEASES

The present invention relates to piperidine derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

The $P2X_7$ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the $P2X_7$ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1β (IL-1β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and L-selectin shedding (lymphocytes). $P2X_7$ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells) and hepatocytes.

It would be desirable to make compounds effective as $P2X_7$ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the $P2X_7$ receptor may play a role.

In accordance with the present invention, there is therefore provided a compound of formula (I):



(I)

where

A is phenyl or a 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from O, N or S; and optionally substituted by C_{1-6}alkyl, halogen, nitro, amino, alkylamino, CF_3, SO_2Me, $NHSO_2Me$ or cyano;

B is C=O, NH or SO_2;

X is C=O, CH(Me), O or $(CH_2)p$ where p is 0 or 1;

Y is O, CH_2, NH or S;

Z is C=O or SO_2, provided that when Z is C=O, then Y is O, CH_2 or S;
R is hydrogen or C_{1-6}alkyl;
R^1 is hydrogen, halogen;
R^2 is phenyl optionally substituted by CO_2H, CO_2alkyl, $CONH_2$ or R^2 is OH, NHR^3, $NHCH(R^4)(CHR^5)_nR^6$, NH-R^7-R^8, SO_2NHalkyl, NHCOalkyl, $NHSO_2$alkyl, morpholine, NR^9R^{10}, piperazine substituted by phenyl, alkoxyphenyl, pyridyl or fluorophenyl;
n is 0, 1 or 2;
R^3 is hydrogen, a bi- or tricyclic saturated ring system optionally containing a nitrogen atom, piperidinyl, alkylpyrollidine, ethynylcyclohexyl, a 5-membered aromatic ring containing 2 or 3 heteroatoms, C_{4-6} cycloalkyl optionally substituted by alkyl, cyano or hydroxy, or C_{1-8} alkyl optionally containing an oxygen atom in the alkyl chain and being optionally substituted by one or more substituents selected from ethynyl, cyano, fluoro, di-alkylamino, hydroxy, thioalkyl, CO_2R^{11} or $CONH_2$;
R^4 is hydrogen or alkyl optionally substituted by hydroxy or alkoxy;
R^5 is hydrogen or hydroxy;
R^6 is CO_2R^{11}, $NHCO_2R^{12}$, $CONH_2$ or a 5 or 6-membered saturated ring containing an oxygen atom, a 5-membered heterocyclic ring containing one or two heteroatoms selected from O, N or S, or phenyl optionally substituted by one or more groups selected from alkyl, hydroxy, amino, alkoxy, or nitro;
R^6 is alkyl;
R^7 is a cyclopentane ring;
R^8 is phenyl;
$R^9$and R^{10} are independently hydrogen, benzyl, alkenyl, cycloalkyl, alkyl optionally substituted by hydroxy, alkoxy, cyano, dialkylamino, phenyl, pyridyl or CO_2R^{11} or R^9 and R^{10} together form a 5- to 7-membered saturated or partially saturated ring optionally containing a further heteroaton and optionally substituted by one or more groups selected from alkyl (optionally containing an oxygen atom in the chain and optionally substituted by hydroxy), COalkyl, CO_2R^{11}, $COR^{13}R^{14}$, CHO or piperidine,
R^{11} is hydrogen or alkyl;
R^{12} is alkyl; and
R^{13} and R^{14} are independently hydrogen or alkyl,
and pharmaceutically acceptable salts and solvates thereof.

In the context of the present specification, unless otherwise indicated, an alkyl substituent or alkyl moiety in a substituent group may be linear or branched and may contain up to 6

carbon atoms, examples of which include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl and n-hexyl.

Suitably A is phenyl or a 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from O, N or S; and optionally substituted by C_{1-6}alkyl, halogen, nitro, amino, alkylamino, CF_3, SO_2Me, $NHSO_2Me$ or cyano. Examples of suitable 5- or 6-membered heterocyclic rings include . Preferably A is optionally substituted phenyl, more preferably A is phenyl substituted by a nitro group.

Suitably B is C=O, NH or SO_2. Preferably B is C=O.

Suitably X is C=O, CH(Me), O or $(CH_2)p$ where p is 0 or 1, Y is O, CH_2, NH or S and Z is C=O or SO_2. Examples of groups formed by X, Y and Z include benzoxazinone and dihydroquinoline. Preferably X is CH_2, Y is O and Z is C=O such that X, Y and Z together form part of a benzoxazinone ring.which can be optionally substituted by methyl.

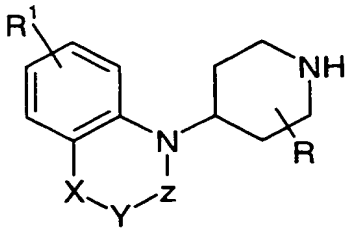
Suitably R is hydrogen or C_{1-6}alkyl, preferably R is hydrogen.

Suitably R^1 is hydrogen or halogen, preferably R^1 is hydrogen.

Suitably R^2 is phenyl optionally substituted by CO_2H, CO_2alkyl, $CONH_2$ or R^2 is OH, NHR^3, $NHCH(R^4)(CHR^5)_nR^6$, NH-R^7-R^8, SO_2NHalkyl, NHCOalkyl, $NHSO_2$alkyl, morpholine, NR^9R^{10}, piperazine substituted by phenyl, alkoxyphenyl, pyridyl or fluorophenyl. Preferably R^2 is NR^9R^{10} where one of R^9 or R^{10} is hydrogen and the other is alkyl such as $CH(CH_3)_2$.

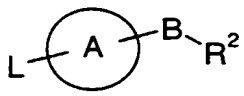
Particularly preferred compounds of the invention include those exemplified herein both in free base form as well as all pharmaceutically acceptable salts and/or solvates thereof.

According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

where R, R^1, X, Y and Z are as defined in formula (I) or a protected derivative thereof, with a compound of formula (III):



(III)

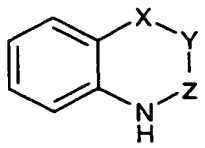
where B and R^2 are as defined in formula (I) or a protected derivative thereof, and L is a leaving group, and optionally thereafter in any order:

- converting one or more functional groups into further functional groups
- removing any protecting groups
- forming a pharmaceutically acceptable salt or solvate.

Examples of suitable leaving groups L include halogen, OMs and OTs. Preferably L is halogen, in particular chloro.

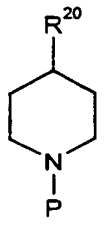
The reaction of compounds of formula (II) and (III) is preferably carried out in the presence of an organic amine such as a trialkylamine, for example triethylamine. The reaction is preferably carried out in an inert solvent such as NMP, DMF or dioxan preferably at elevated temperature, for example at the reflux temperature of the reaction mixture.

Compounds of formulae (II) can be prepared as follows:
(a) by reacting a compound of formula (IV):



(IV)

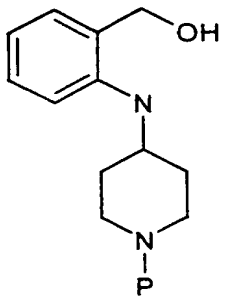
in which X, Y and Z are as defined in formula (II) or are protected derivatives thereof, with a compound of formula (V):



(V)

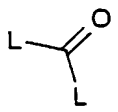
in which R^{20} is a leaving group or an activated hydroxy group, or

(b) by reacting a compound of formula (VI):



(VI)

in which P a protecting group, with a compound of formula (VII):



(VII)

in which the groups L are leaving groups.

Compounds of formulae (IV) and (V) can be reacted under Mitsonobu conditions when R^{20} in compound (V) is an activated hydroxy group. For the reaction of compounds (VI) and (VII), examples of suitable leaving L groups include halogen, in particular chloro, or imidazole. Alternatively triphosgene can be used. Suitable protecting groups for compounds (V) and (VI) include t-butoxy carbonyl (Boc).

Compounds of formula (III), (IV), (V) and (VII) are prepared using lterature procedures or are commercially available.

Functional groups can be converted into further functional groups using procedures known in the art. For example a carboxylic acid group can be converted into an ester or amide using standard chemistry.

Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in `Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and `Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

Deprotection can be carried out using methods generally known in the art.

All novel intermediates form a further aspect of the invention.

The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compounds of the present invention are advantageous in that they possess pharmacological activity and have utility as modulators of $P2X_7$ receptor activity. They are therefore indicated as pharmaceuticals for use in the treatment or prevention of

rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, hyperresponsiveness of the airway, chronic obstructive pulmonary disease (COPD), bronchitis, septic shock, glomerulonephritis, irritable bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myoblastic leukaemia, diabetes, neurodegenerative disease, Alzheimer's disease, meningitis, osteoporosis, burn injury, ischaemic heart disease, stroke, peripheral vascular disease and varicose veins.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

The invention further provides a method of effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis or psoriasis) which comprises administering a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

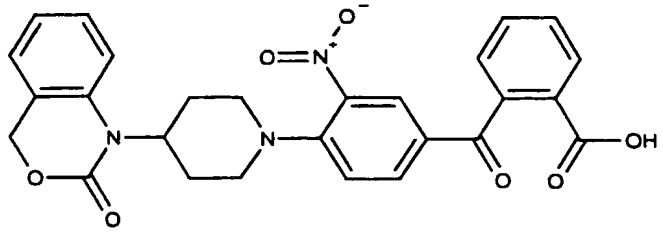
The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The present invention will now be further illustrated by reference to the following examples.

Example 1

2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoic acid



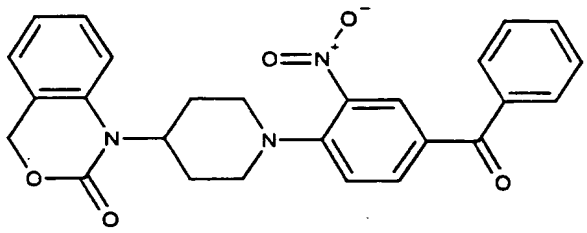
A solution of 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (J.Med. Chem. 1998, 2157) (0.8g), 2-(4-chloro-3-nitrobenzoyl)benzoic acid (0.9g) and triethylamine (0.8ml) in N,N-dimethylformamide (5ml) was stirred at room temperature for 72h. The mixture was partitioned between ethyl acetate and dilute hydrochloric acid, the organic layer was evaporated under reduced pressure. Purification was by chromatography

eluting with 4% methanol/dichloromethane. The residue was triturated from methanol, yield 0.4g as a solid.

MS: APCI(+ve) 502(M+1)
1H NMR: δ (CDCl3/DMSO-d6) 8.13-8.05(2H, m), 7.80(1H, d), 7.70-7.57(2H, m), 7.43-7.33(2H, m), 7.23-7.09(4H,m), 5.12(2H, s), 4.20-4.08(1H, m), 3.55(2H, d), 3.21(2H, t), 2.90-2.80(2H, m), 1.97(2H, d)
MP:243-4°C

Example 2

1-{1-[2-Nitro-4-(phenylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one

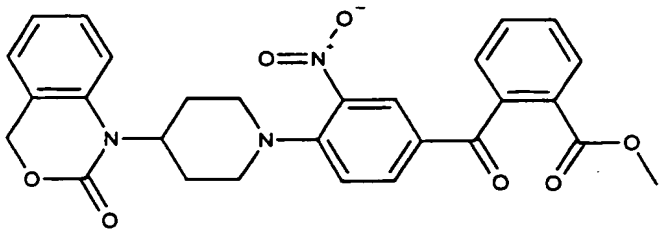


The title compound was prepared from 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.3g) and 4-chloro-3-nitrobenzophenone (0.29g) using the method of example 1. Yield 0.25g as a solid.

MS: APCI(+ve) 458(M+1)
1H NMR: δ (CDCl3/DMSO-d6) 8.28(1H, d), 7.98(1H, dd), 7.78-7.75(2H, m), 7.63-7.60(1H, m), 7.53-7.50(2H,m), 7.38(1H, t), 7.22-7.10(4H, m), 5.11(2H, s), 4.25-4.19(1H, m), 3.61(2H, d), 3.23(2H, t), 2.93-2.84(2H, m), 1.98(2H, d)
MP:272-3°C

Example 3

Methyl 2-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoate

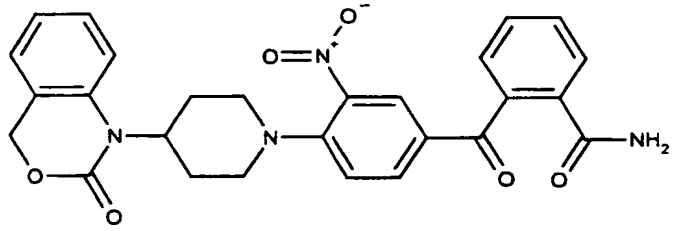


The product from example 1 was added to methanolic hydrogen chloride and the mixture stirred overnight. The solvent was removed under reduced pressure and the residue purified by chromatography. Yield 0.03g.

MS: APCI(+ve) 516(M+1)
1H NMR: δ ($CDCl_3$) 8.10-8.07(2H, m), 7.91(1H, dd), 7.68-7.57(2H, m), 7.39-7.35(2H, m), 7.19-7.09(4H, m), 5.29(2H, s), 4.22-4.17(1H, m), 3.75(3H, s), 3.57(2H, d), 3.20(2H, t), 2.90-2.81(2H, m), 1.96(2H, d)
MP:177-9°C

Example 4

2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzamide

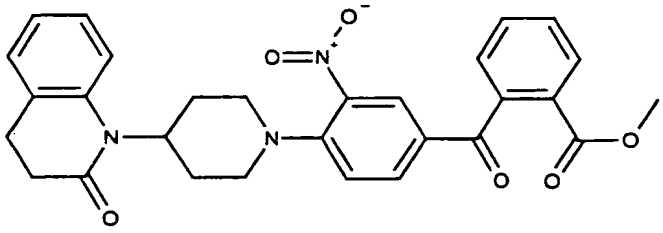


A solution of the product from example 1 (0.9g) and carbonyldiimidazole (1.1 equiv.) in dichloromethane (4ml) was stirred at room temperature for 1h, poured onto aqueous ammonia and stirred for a further 1h. The mixture was extracted with ethyl acetate, the organics washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 2.5% methanol/dichloromethane. Yield 0.01g as a solid.

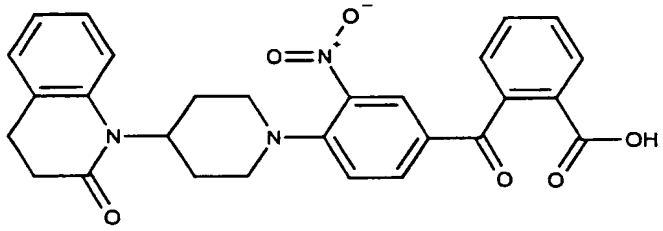
MS: APCI(+ve) 501(M+1)
1H NMR: δ ($CDCl_3$) 8.08(1H, d), 7.64(1H, d), 7.58-7.34(5H, m), 7.20-7.07(4H, m), 7.03(1H, s), 5.08(2H, s), 4.35(1H, s), 4.21-4.13(1H, m), 3.42(2H, d), 3.04(2H, t), 2.86-2.74(2H, m), 1.90(2H, d)
MP:180-2°C

Example 5

Methyl 2-({3-nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoate



(i) 2-({3-Nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoic acid



The product was prepared from 1-piperidin-4-yl-3,4-dihydroquinolin-2(1H)-one (Chem. Pharm. Bull. (1996), 44(4), 725-33) (0.45g) and 2-(4-chloro-3-nitrobenzoyl)benzoic acid (0.6g) using the method of example 1. Used crude.

(ii) Methyl 2-({3-nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoate

The title compound was prepared from the product from step (i) (0.2g) which was added to methanolic hydrogen chloride and stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and aqueous sodium hydrogencarbonate solution. The organics were separated, dried and evaporated under reduced pressure. Purification was by chromatography to yield 0.18g of a solid.

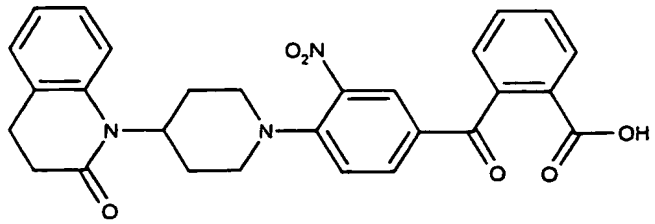
MS: APCI(+ve) 514(M+1)

1H NMR: δ ($CDCl_3$) 8.09-8.07(2H, m), 7.92(1H, dd), 7.68-7.56(2H, m), 7.37(1H, d), 7.26-7.13(4H, m), 7.03(1H, t), 4.50-4.46(1H, m), 3.74(3H, s), 3.53(2H, d), 3.18(2H, t), 2.86-2.75(4H, m), 2.61-2.57(2H, m), 1.84(2H, d)

MP:112-3°C

Example 6

2-({3-Nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoic acid



Lithium hydroxide hydrate (3 equiv.) was added to a mixture of the product from example 5 step (ii) (0.15g) in methanol/water (5.5ml, 10:1) and stirred overnight at room temperature. The solvent was removed under reduced pressure, the residue dissolved in water and neutralised with dilute hydrochloric acid. The mixture was extracted with ethyl acetate, dried and evaporated under reduced pressure. The residue was triturated with ether and the solid collected. Yield 0.06g.

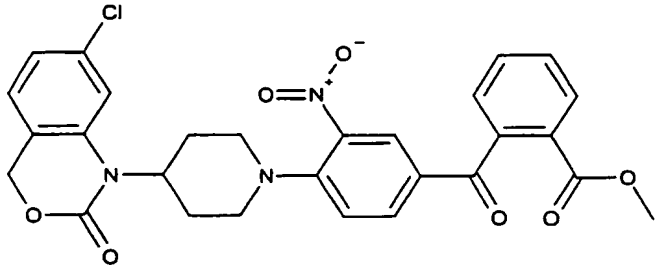
MS: APCI(+ve) 500(M+1)

1H NMR: δ ($CDCl_3$) 8.11(2H, m), 7.86(1H, dd), 7.71(1H, m), 7.59(1H, m), 7.38(1H, dd), 7.18(4H, m), 7.01(1H, m), 4.48(1H, m), 3.51(2H, m), 3.16(2H, m), 2.83(4H, m), 2.27(2H, m), 1.84(2H, m)

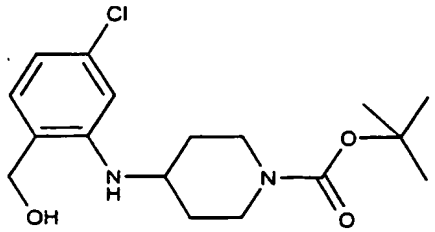
MP:201-203°C

Example 7

Methyl 2-({4-[4-(7-chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-3-nitrophenyl}carbonyl)benzoate



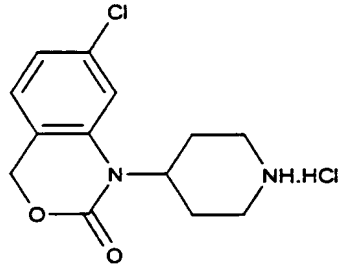
(i) 1,1-Dimethylethyl 4-{[5-chloro-2-(hydroxymethyl)phenyl]amino}piperidine-1-carboxylate



N-tert-Butoxycarbonyl-4-piperidone (5.8g), 2-amino-5-chlorobenzyl alcohol (5.02g) and acetic acid (4ml) in toluene (200ml) were heated under reflux using a Dean-Stark trap for 1.5h. The solvent was evaporated under reduced pressure to ~100ml, tetrahydrofuran (100ml) added followed by sodium cyanoborohydride (6.3g). Acetic acid (3ml) was added dropwise to this mixture which was stirred at room temperature for 96h. The solvents were removed under reduced pressure and the residue partitioned between ethyl acetate and aqueous sodium hydrogencarbonate solution. The organics were dried, evaporated under reduced pressure and the residue triturated with dichloromethane/isohexane. Yield 7.5g.

MS: APCI(+ve) 500(M+1)

(ii) 7-Chloro-1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride



Triphosgene (1.6g) was added to a stirred solution of the product from step (i) (5g), N,N-diisopropylethylamine (5.2ml) in tetrahydrofuran (50ml) at 0°C. The mixture was stirred at room temperature for 16h, the precipitate filtered and the filtrate evaporated under reduced pressure. Purification was by chromatography eluting with 20% ethyl acetate/toluene. The product was dissolved in dichloromethane then a solution of hydrogen chloride in 1,4-dioxane added. After 2h the solvent was removed under reduced pressure to yield a solid. Used directly.

(iii) Methyl 2-({4-[4-(7-chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-3-nitrophenyl}carbonyl)benzoate

Methyl 2-[(4-chloro-3-nitrophenyl)carbonyl]benzoate (0.5g), the product from step (ii) (0.47g) and triethylamine (0.5ml) in N,N-dimethylformamide (2.5ml) were heated at 60°C

overnight. The mixture was evaporated under reduced pressure and the residue purified by chromatography eluting with 25% ethyl acetate/toluene. Yield 0.7g of a solid.

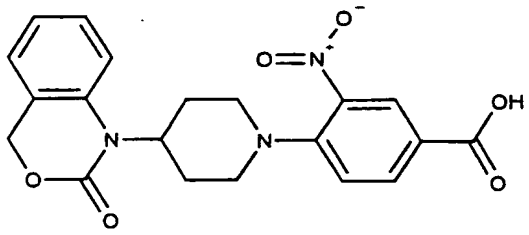
MS: APCI(+ve) 550(M+1)

1H NMR: δ (DMSO-d6) 8.00-7.97(2H, m), 7.80-7.72(2H, m), 7.70-7.65(1H, m), 7.46(1H, d), 7.40-7.30(4H, m), 5.12(2H, s), 4.20-4.10(1H, m), 3.64(3H, s), 3.49(2H, br d), 3.26(2H, br t), 2.70-2.60(2H, m), 1.97-1.91(2H, m)

MP:90-2°C

Examples 8-114

(i) 3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzoic acid



A solution of 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (1.0g), 1,1-dimethylethyl 4-chloro-3-nitrobenzoate (0.95g) and triethylamine (0.8g) in N,N-dimethylformamide (10ml) was stirred at room temperature overnight. The mixture was partitioned between ethyl acetate and water. The organic layer was dried, and evaporated under reduced pressure. Purification was by chromatography eluting with 1:2 ethyl acetate-isohexane. The residue was dissolved in formic acid (5ml) stirred overnight at room temperature, heated at 55°C for 2h, then evaporated under reduced pressure. The residue was triturated with ether, yield 0.85g as a solid.

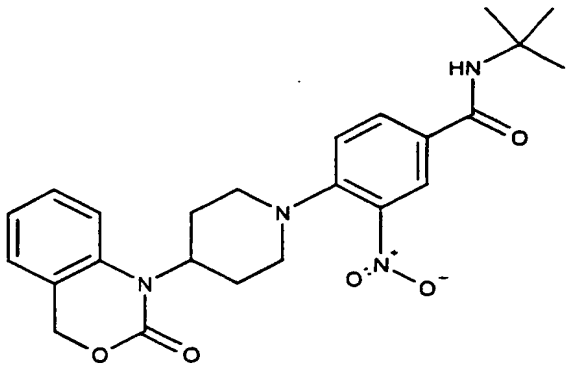
MS: APCI(+ve) 398(M+1)

(ii) Examples 8-114

Carbonyldiimidazole (0.2g) was added to a solution of the product from step (i) (0.4g) in N,N-dimethylformamide (25ml) and stirred at room temperature for 2.5h. The activated acid (0.1ml) the appropriate amine (5 equivalents) and triethylamine (5 equivalents) in 1-methyl-2-pyrrolidinone (0.1ml) were left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

Example 8

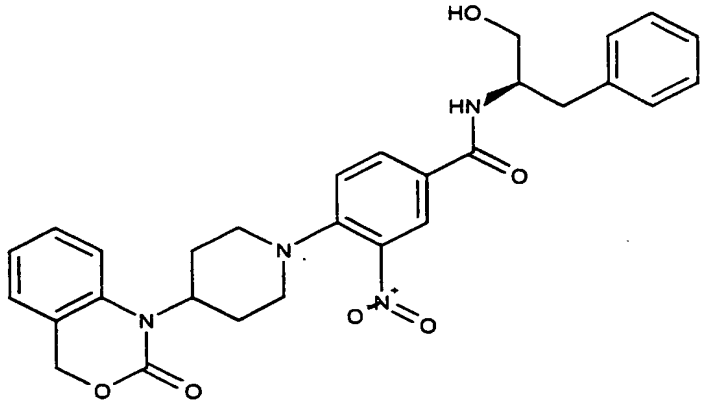
N-(1,1-Dimethylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 453(M+1)

Example 9

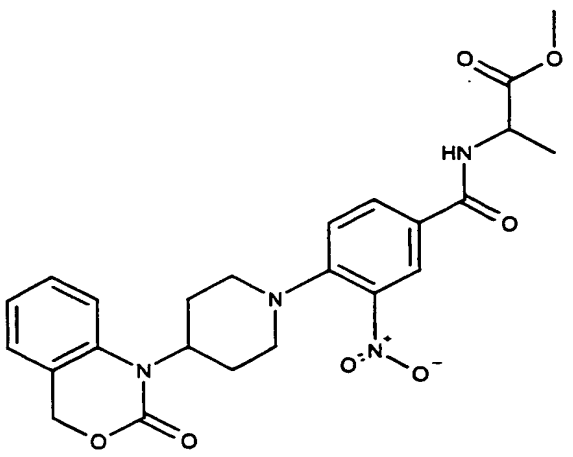
N-[(1R)-2-Hydroxy-1-(phenylmethyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 531(M+1)

Example 10

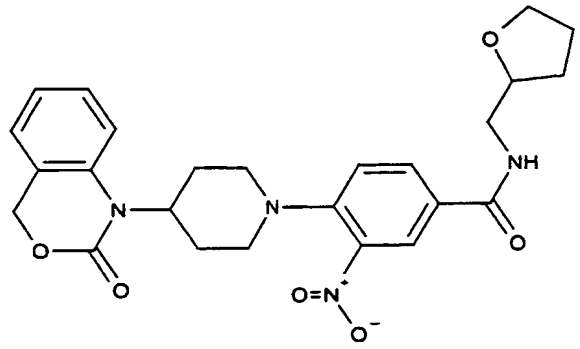
Methyl 2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propanoate



MS: APCI(+ve) 483(M+1)

Example 11

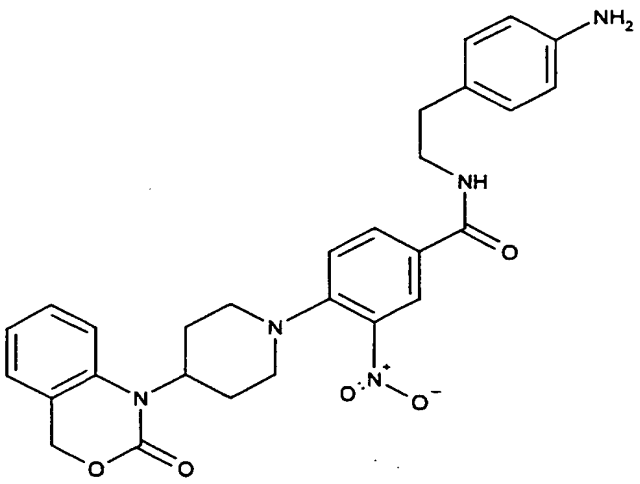
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(tetrahydrofuran-2-ylmethyl)benzamide



MS: APCI(+ve) 481(M+1)

Example 12

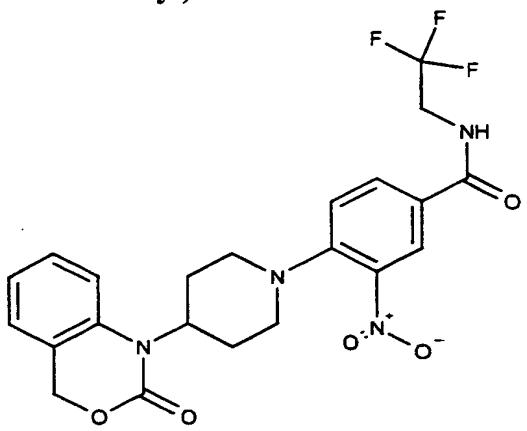
N-[2-(4-Aminophenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 516(M+1)

Example 13

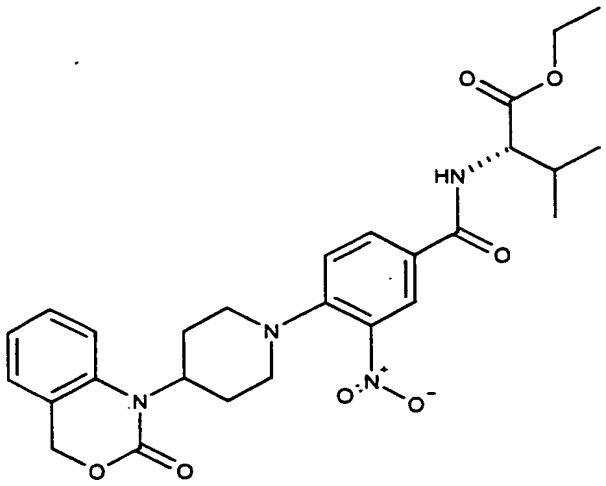
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)benzamide



MS: APCI(+ve) 479(M+1)

Example 14

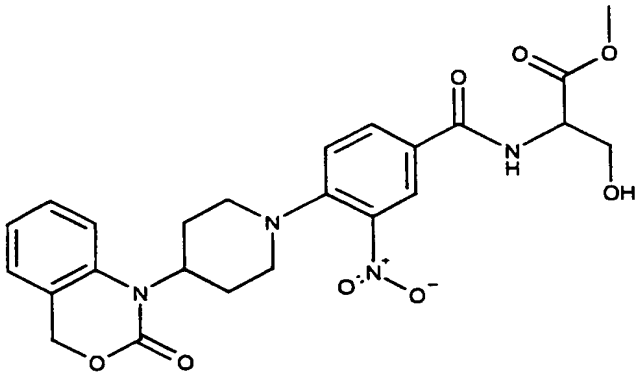
Ethyl (2S)-3-methyl-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]butanoate



MS: APCI(+ve) 525(M+1)

Example 15

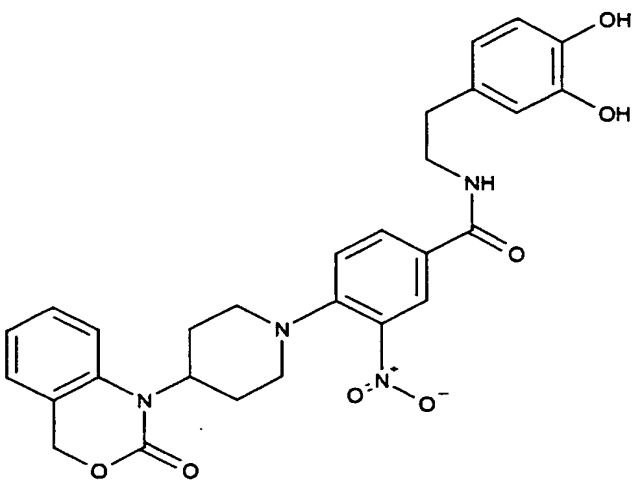
Methyl 3-hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propanoate



MS: APCI(+ve) 499(M+1)

Example 16

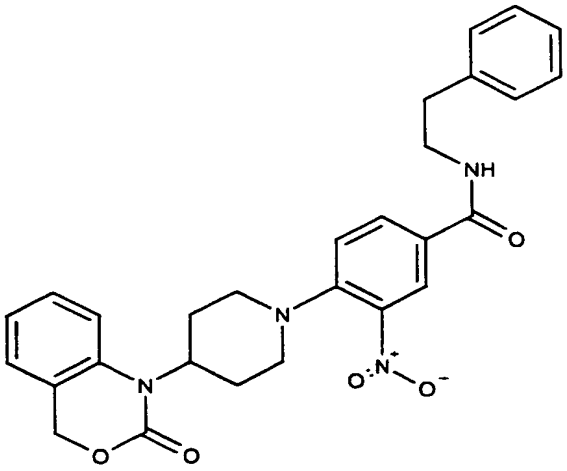
N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 533(M+1)

Example 17

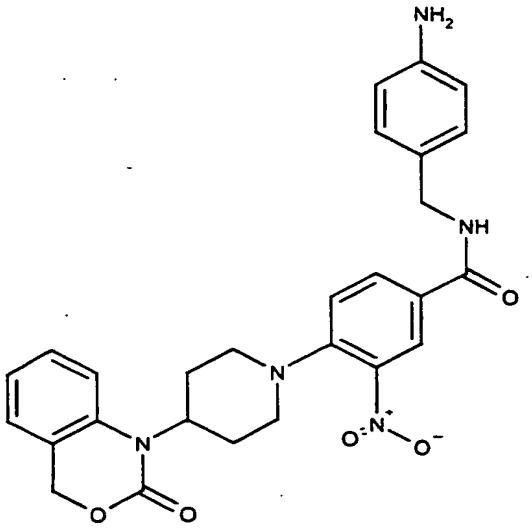
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-phenylethyl)benzamide



MS: APCI(+ve) 501(M+1)

Example 18

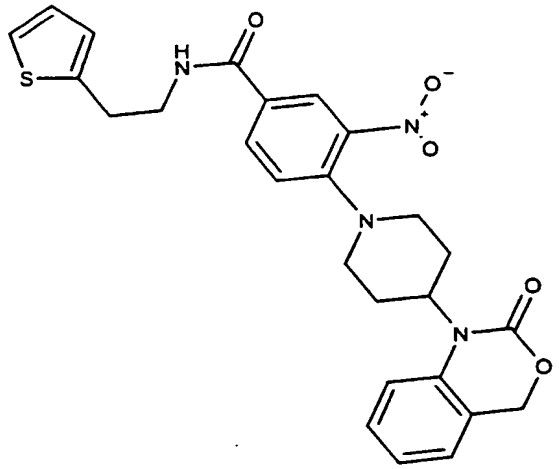
N-[(4-Aminophenyl)methyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 502(M+1)

Example 19

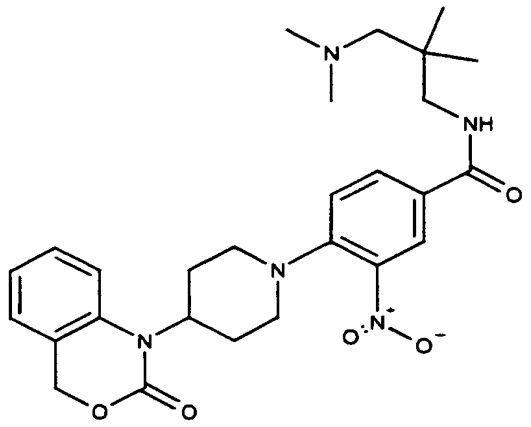
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-thien-2-ylethyl)benzamide



MS: APCI(+ve) 507(M+1)

Example 20

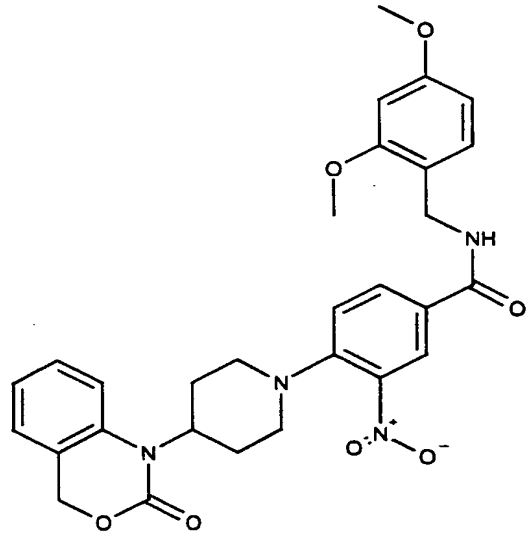
N-[3-(Dimethylamino)-2,2-dimethylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 510(M+1)

Example 21

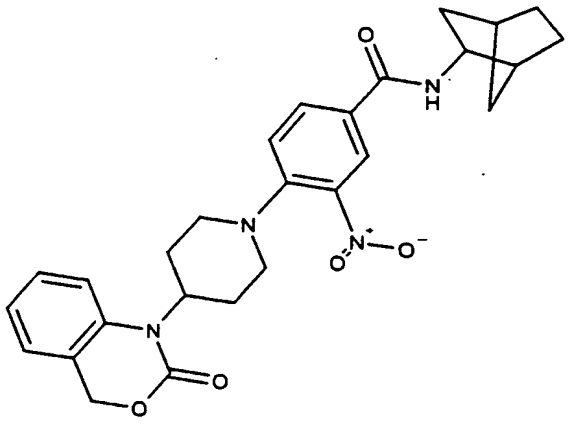
N-{[2,4-Bis(methyloxy)phenyl]methyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 547(M+1)

Example 22

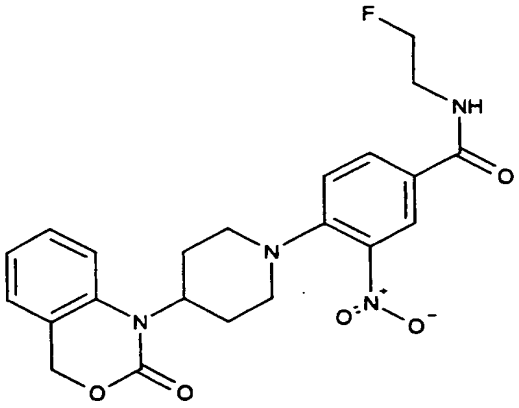
N-Bicyclo[2.2.1]hept-2-yl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 491(M+1)

Example 23

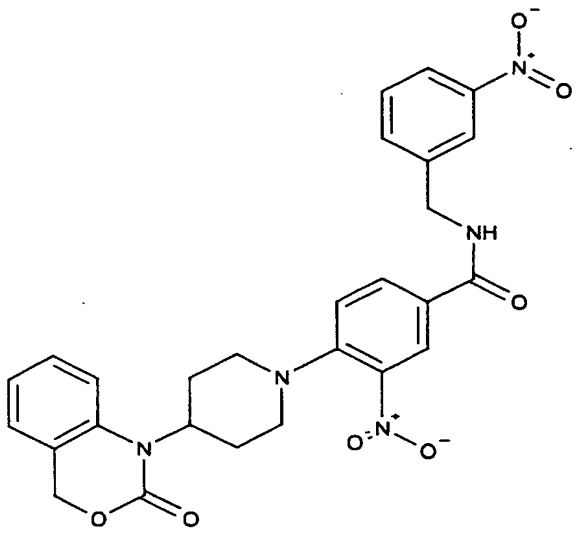
N-(2-Fluoroethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 443 (M+1)

Example 24

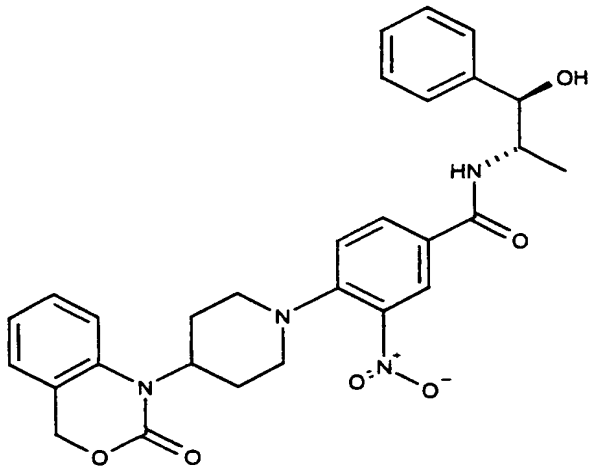
3-Nitro-N-[(3-nitrophenyl)methyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 532(M+1)

Example 25

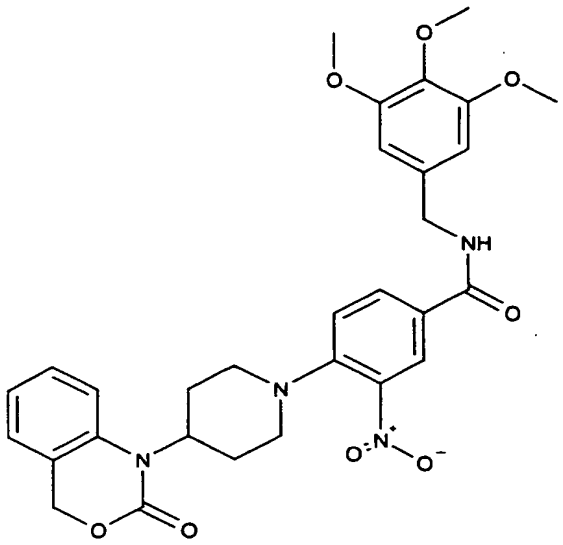
N-[(1S,2R)-2-Hydroxy-1-methyl-2-phenylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 531(M+1)

Example 26

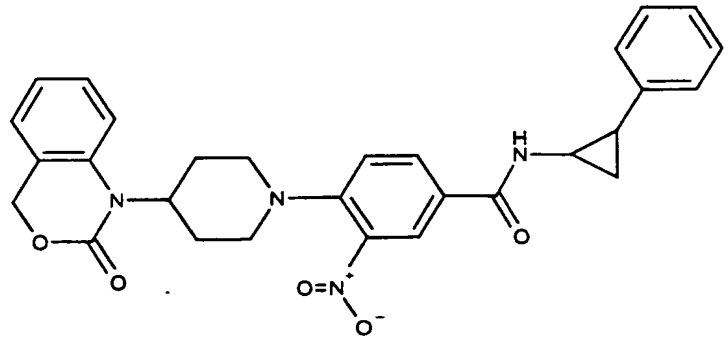
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-{[3,4,5-tris(methyloxy)phenyl]methyl}benzamide



MS: APCI(+ve) 577(M+1)

Example 27

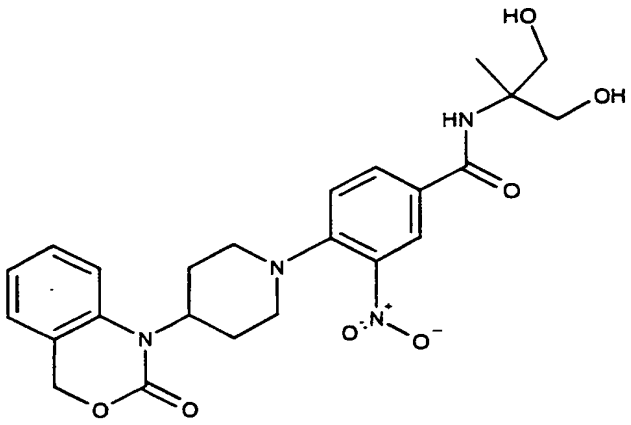
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-phenylcyclopropyl)benzamide



MS: APCI(+ve) 513(M+1)

Example 28

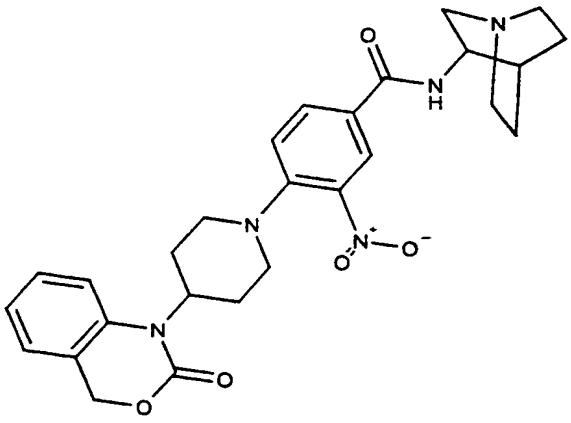
N-[2-Hydroxy-1-(hydroxymethyl)-1-methylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 485(M+1)

Example 29

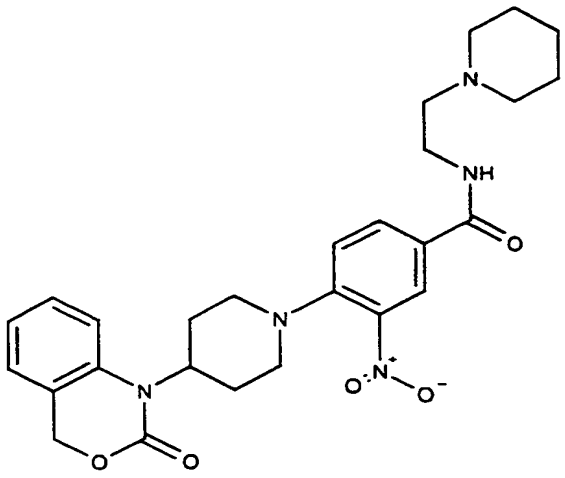
N-(1-Azabicyclo[2.2.2]oct-3-yl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 506(M+1)

Example 30

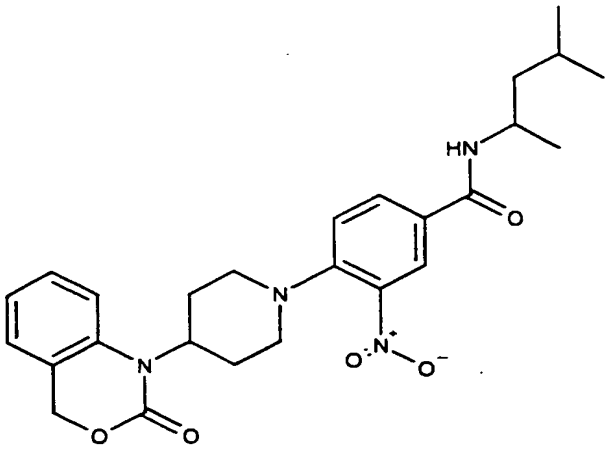
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-piperidin-1-ylethyl)benzamide



MS: APCI(+ve) 508(M+1)

Example 31

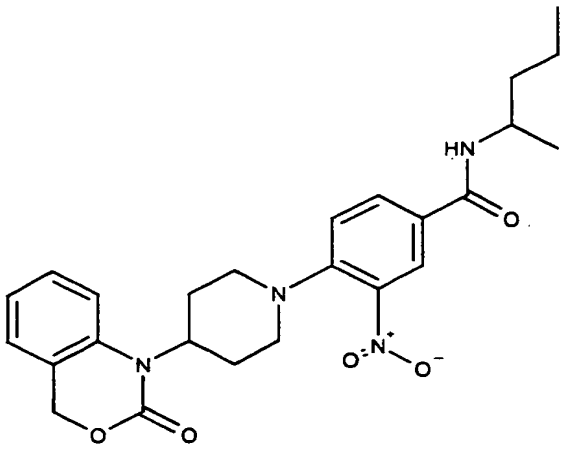
N-(1,3-Dimethylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 481(M+1)

Example 32

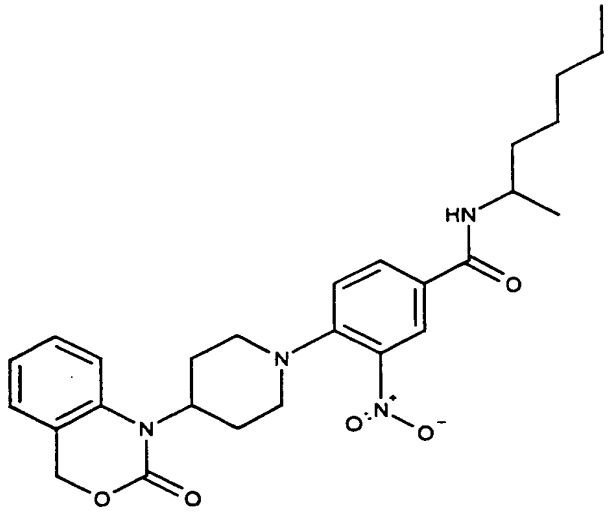
N-(1-Methylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 467(M+1)

Example 33

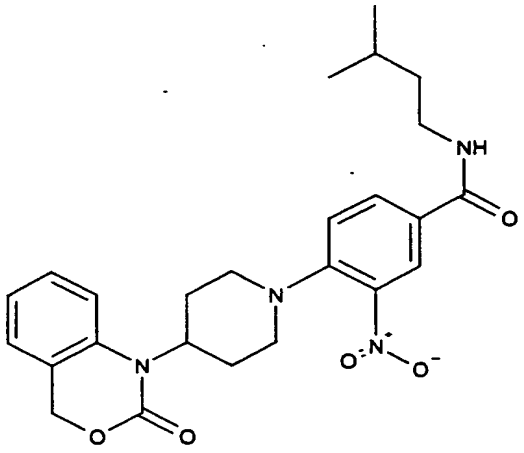
N-(1-Methylhexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 495(M+1)

Example 34

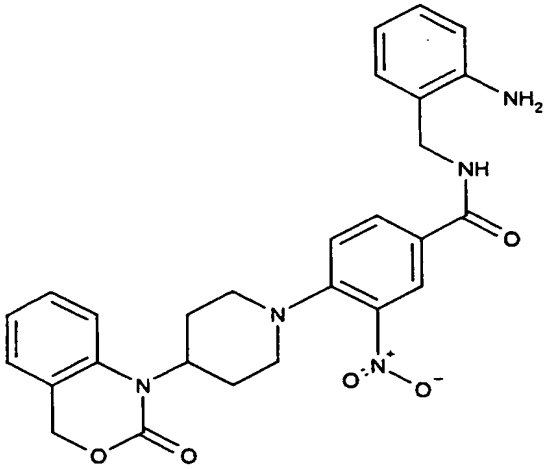
N-(3-Methylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 467(M+1)

Example 35

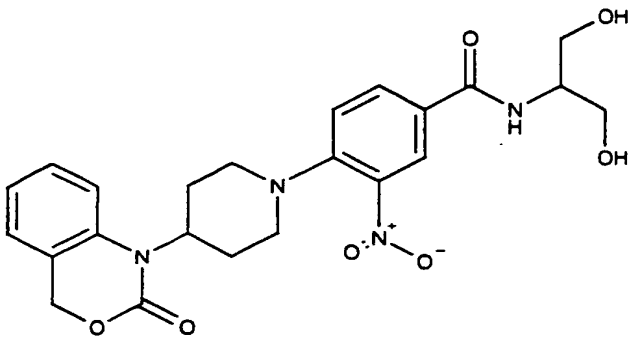
N-[(2-Aminophenyl)methyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 502(M+1)

Example 36

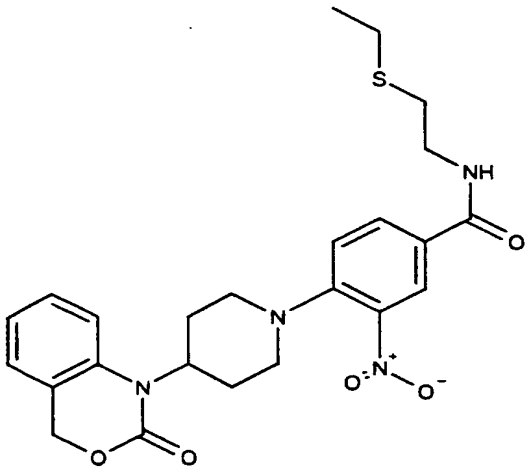
N-[2-Hydroxy-1-(hydroxymethyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 471(M+1)

Example 37

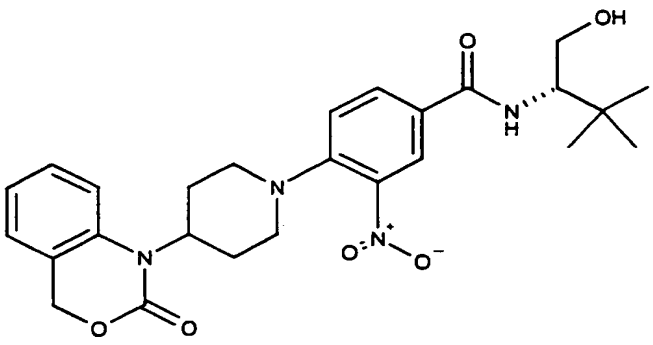
N-[2-(Ethylthio)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 485(M+1)

Example 38

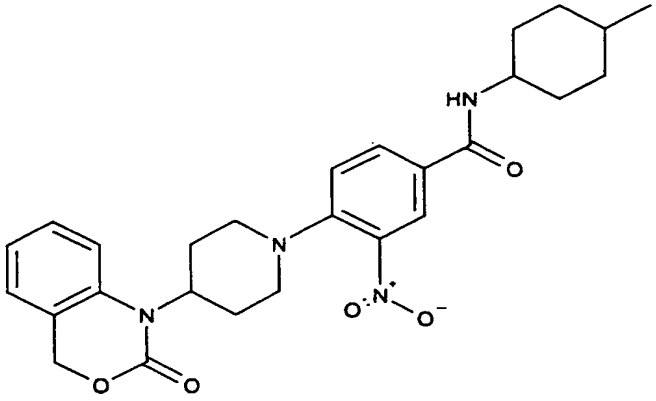
N-[(1S)-1-(Hydroxymethyl)-2,2-dimethylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 497(M+1)

Example 39

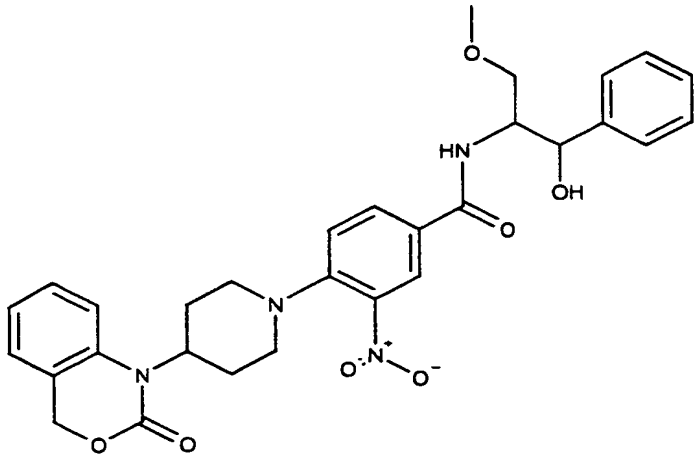
N-(4-Methylcyclohexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 493(M+1)

Example 40

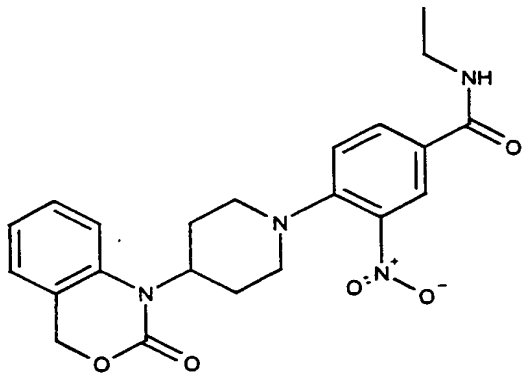
N-{2-Hydroxy-1-[(methyloxy)methyl]-2-phenylethyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 561(M+1)

Example 41

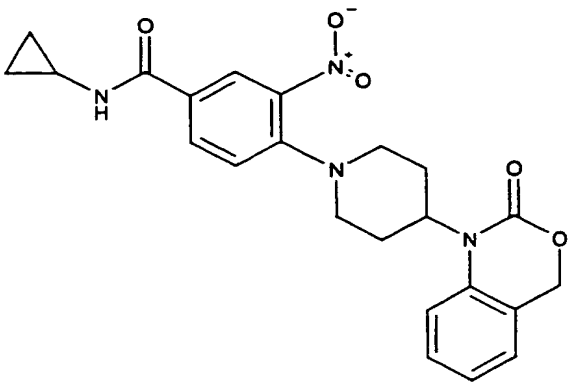
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 425(M+1)

Example 42

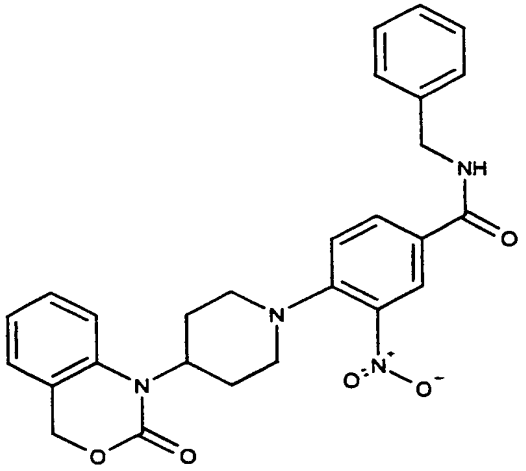
N-Cyclopropyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 437(M+1)

Example 43

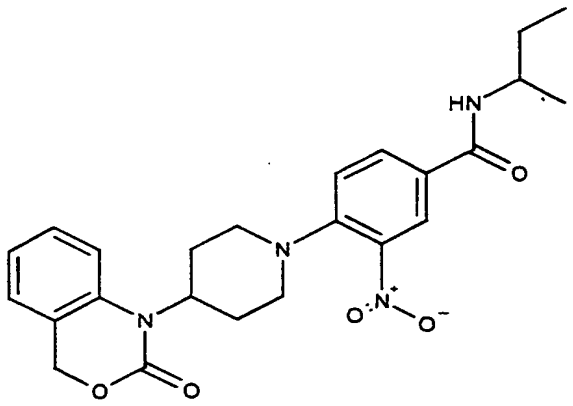
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide



MS: APCI(+ve) 487(M+1)

Example 44

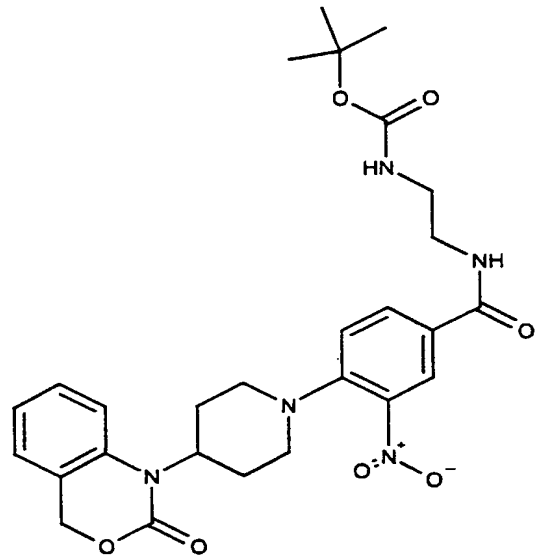
N-(1-Methylpropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 453(M+1)

Example 45

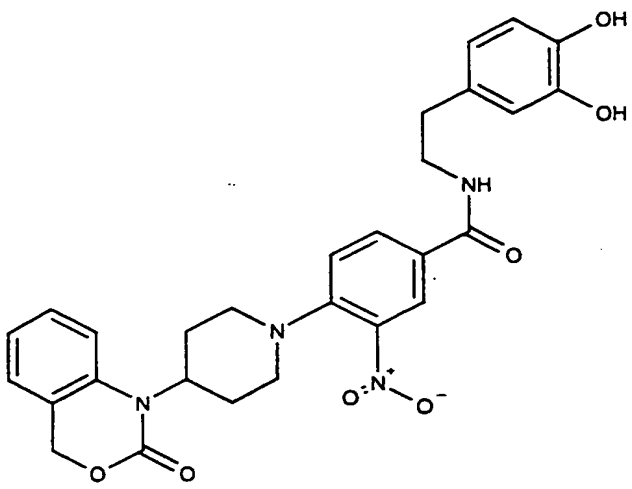
1,1-Dimethylethyl 2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]ethylcarbamate



MS: APCI(+ve) 440(M+1-Boc)

Example 46

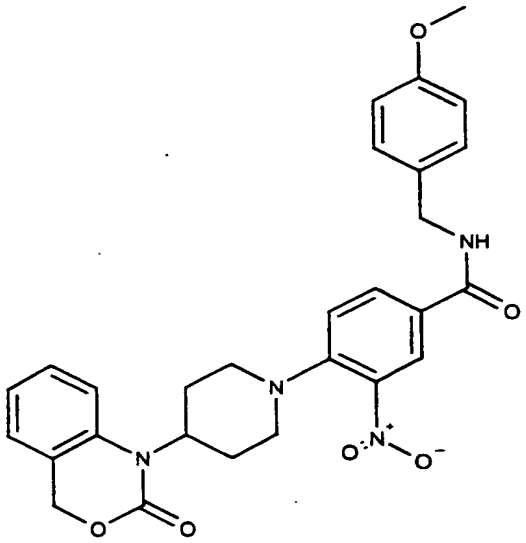
N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 533(M+1)

Example 47

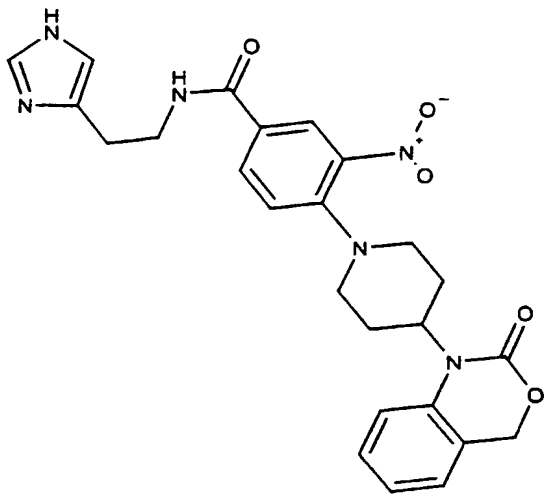
N-{[4-(Methyloxy)phenyl]methyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 517(M+1)

Example 48

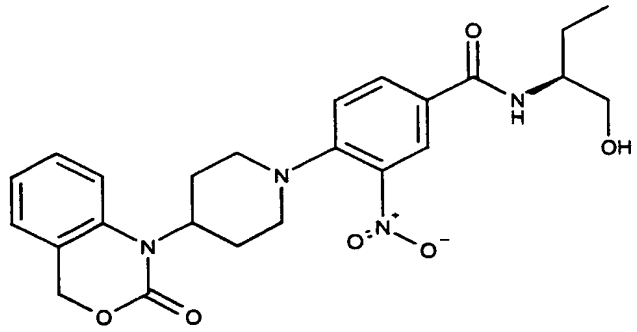
N-[2-(1H-Imidazol-4-yl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 491(M+1)

Example 49

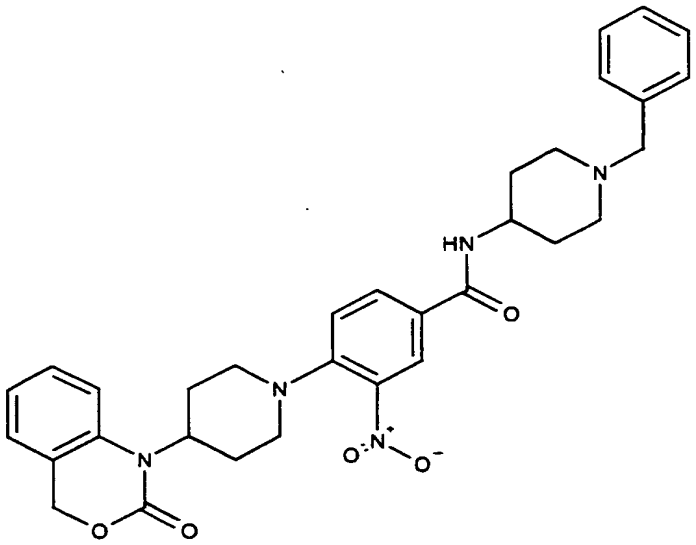
N-[(1S)-1-(Hydroxymethyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 469(M+1)

Example 50

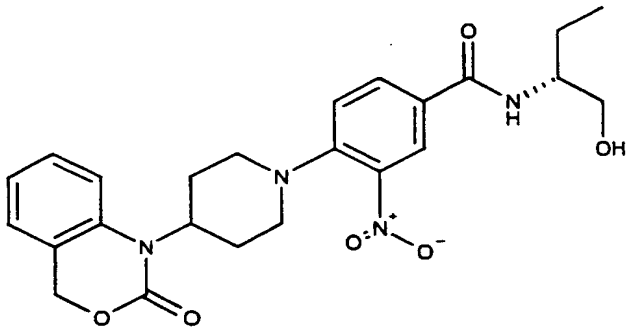
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-[1-(phenylmethyl)piperidin-4-yl]benzamide



MS: APCI(+ve) 570(M+1)

Example 51

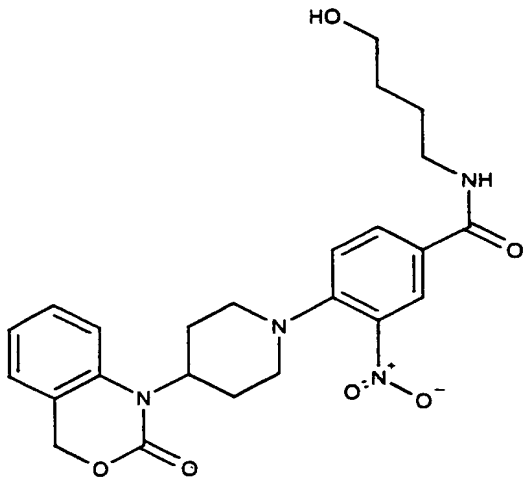
N-[(1R)-1-(Hydroxymethyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 469(M+1)

Example 52

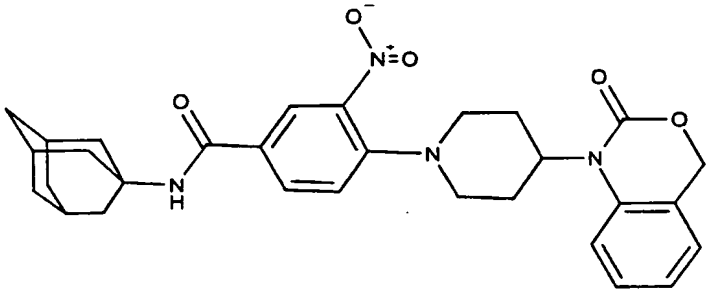
N-(4-Hydroxybutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 469(M+1)

Example 53

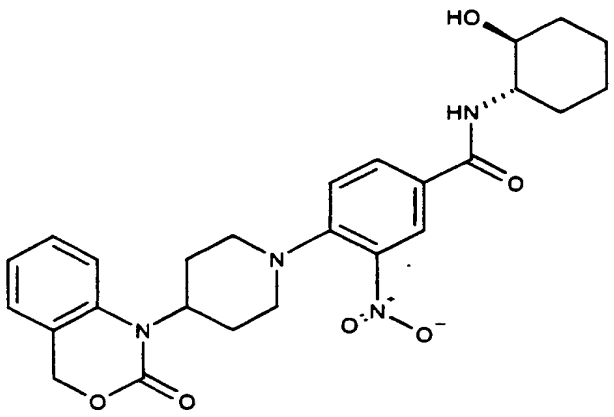
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-tricyclo[3.3.1.1~3,7~]dec-1-ylbenzamide



MS: APCI(+ve) 531(M+1)

Example 54

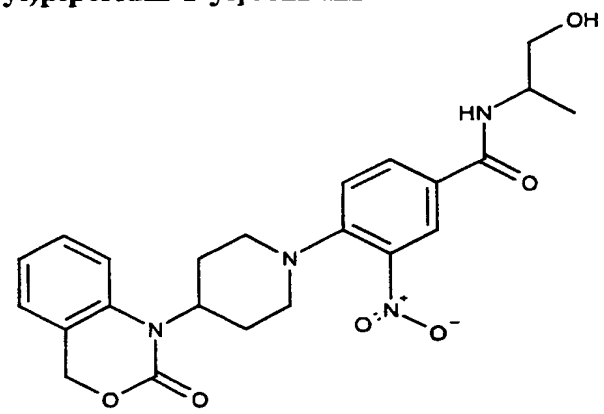
N-[(1S,2S)-2-Hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 495(M+1)

Example 55

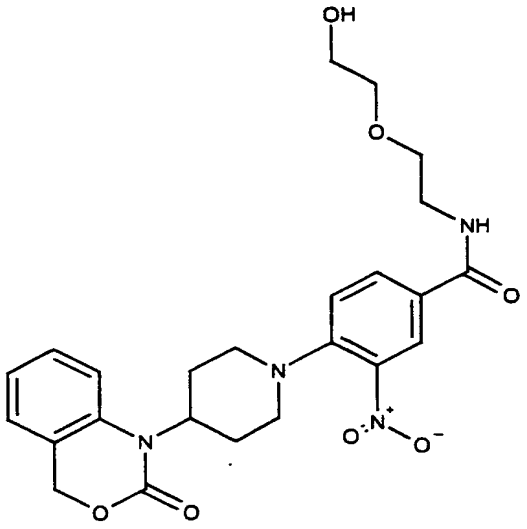
N-(2-Hydroxy-1-methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 455(M+1)

Example 56

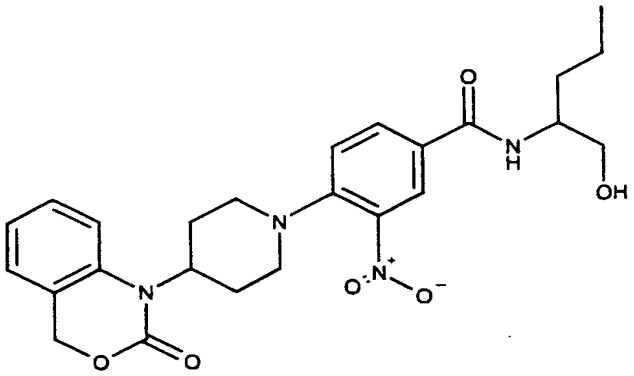
N-{2-[(2-Hydroxyethyl)oxy]ethyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 485(M+1)

Example 57

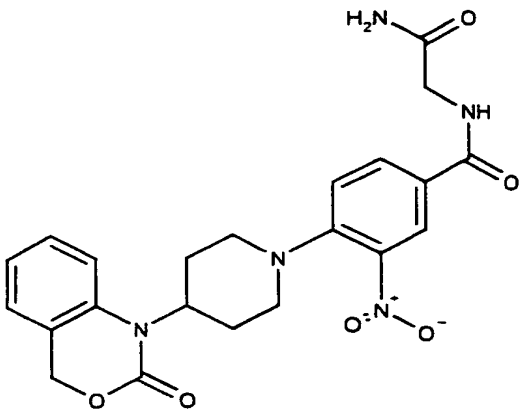
N-[1-(Hydroxymethyl)butyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 483(M+1)

Example 58

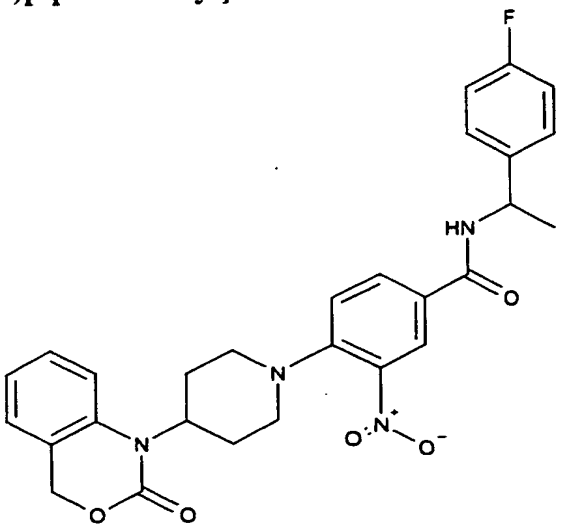
N-(2-Amino-2-oxoethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 454(M+1)

Example 59

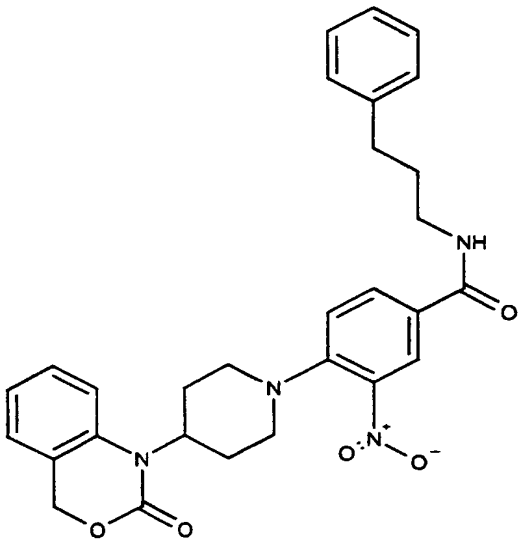
N-[1-(4-Fluorophenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 519(M+1)

Example 60

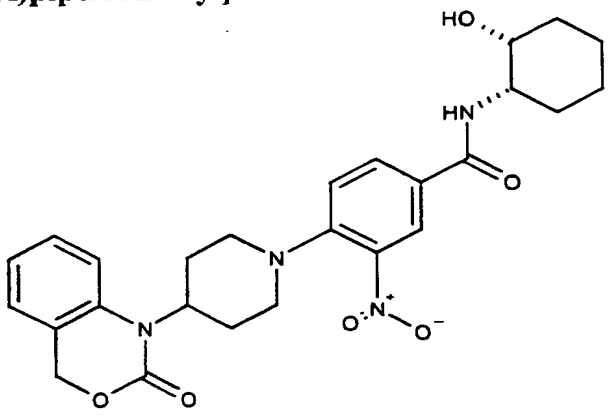
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(3-phenylpropyl)benzamide



MS: APCI(+ve) 515(M+1)

Example 61

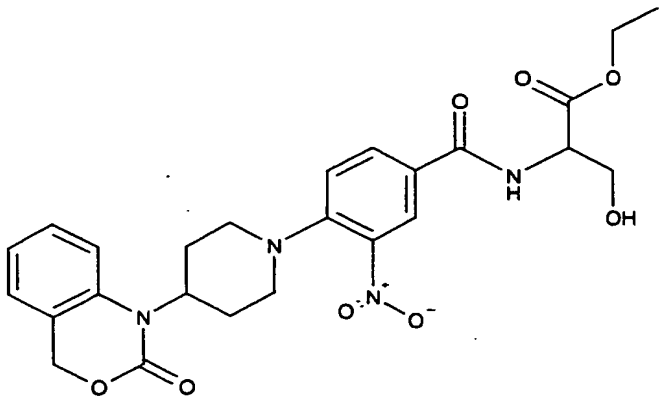
N-[(1S,2R)-2-Hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 495(M+1)

Example 62

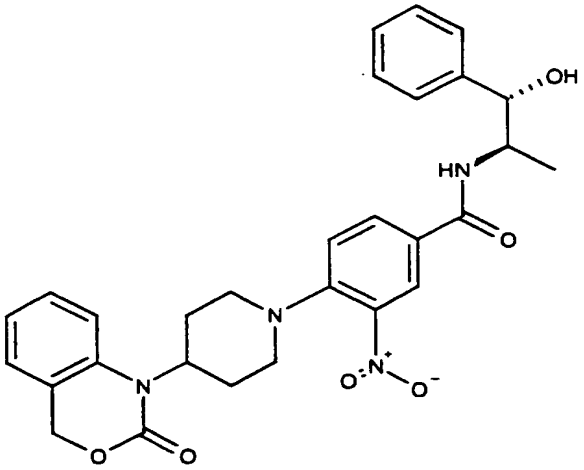
Ethyl 3-hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propanoate



MS: APCI(+ve) 513(M+1)

Example 63

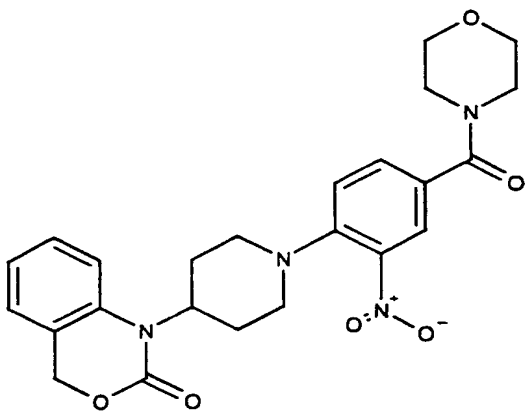
N-[(1R,2S)-2-Hydroxy-1-methyl-2-phenylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 531(M+1)

Example 64

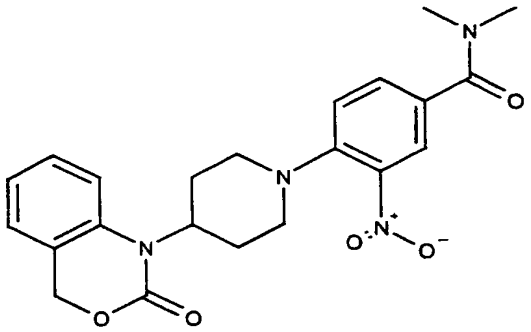
1-{1-[4-(Morpholin-4-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 467(M+1)

Example 65

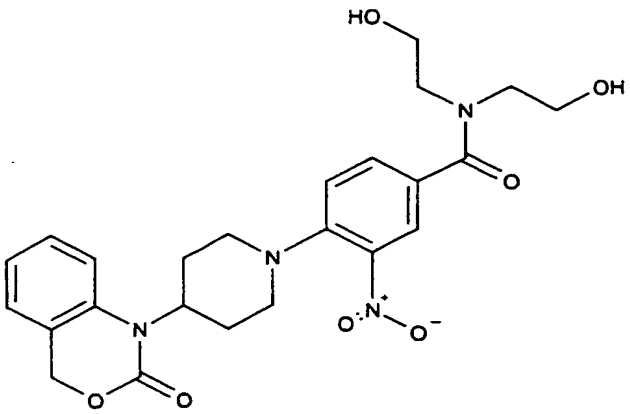
N,N-Dimethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 425(M+1)

Example 66

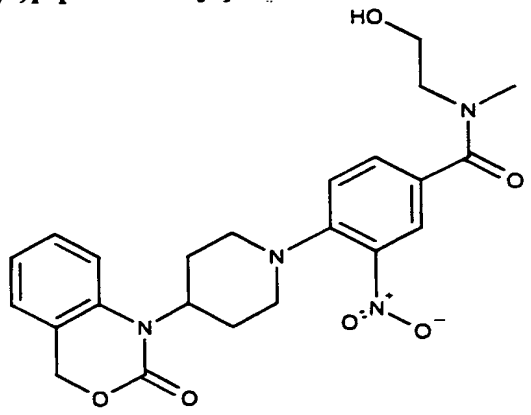
N,N-Bis(2-hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 485 (M+1)

Example 67

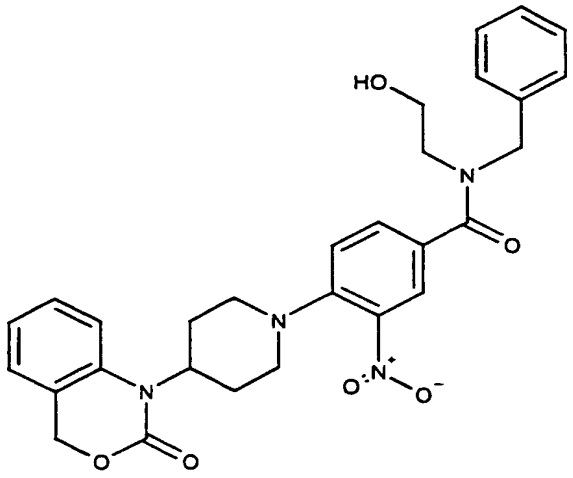
N-(2-Hydroxyethyl)-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 455(M+1)

Example 68

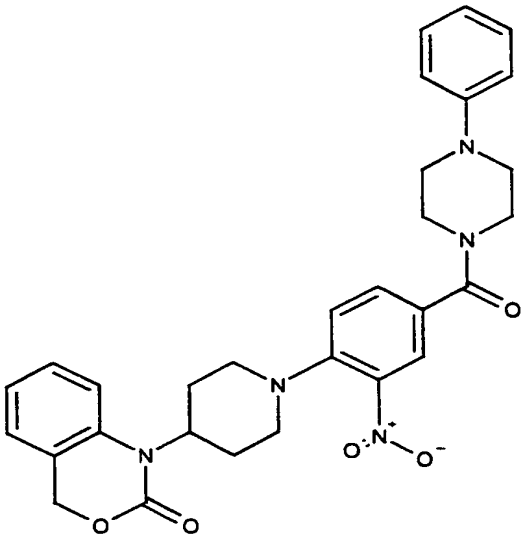
N-(2-Hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide



MS: APCI(+ve) 531 (M+1)

Example 69

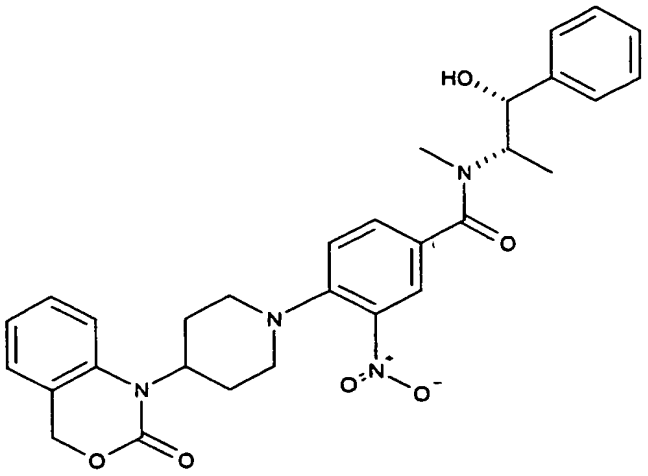
1-(1-{2-Nitro-4-[(4-phenylpiperazin-1-yl)carbonyl]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 542(M+1)

Example 70

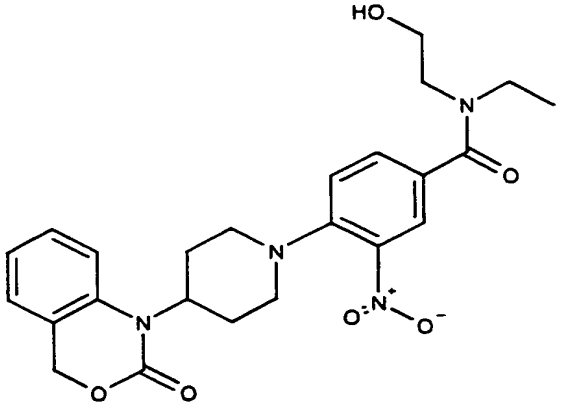
N-[(1S,2R)-2-hydroxy-1-methyl-2-phenylethyl]-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 545(M+1)

Example 71

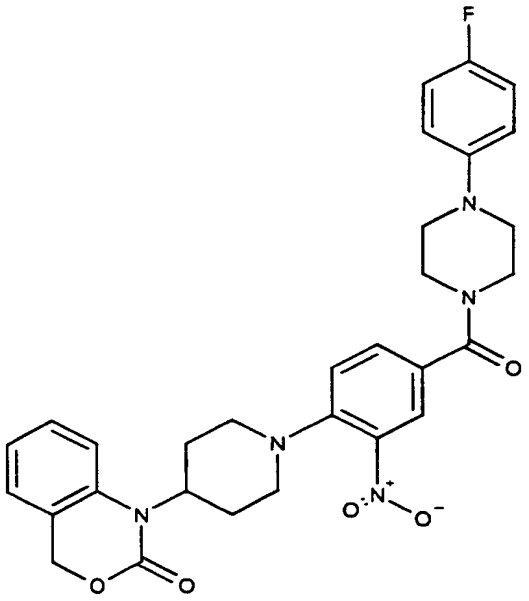
N-Ethyl-N-(2-hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 469(M+1)

Example 72

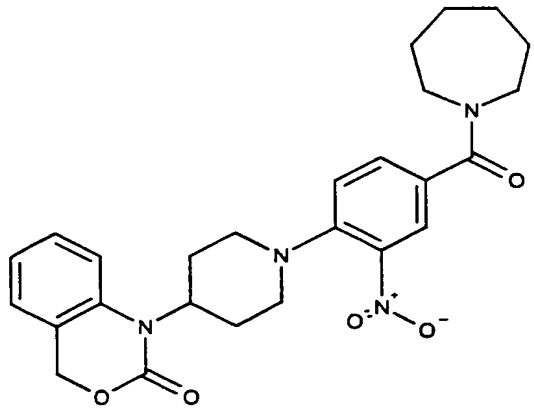
1-[1-(4-{[4-(4-Fluorophenyl)piperazin-1-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 560(M+1)

Example 73

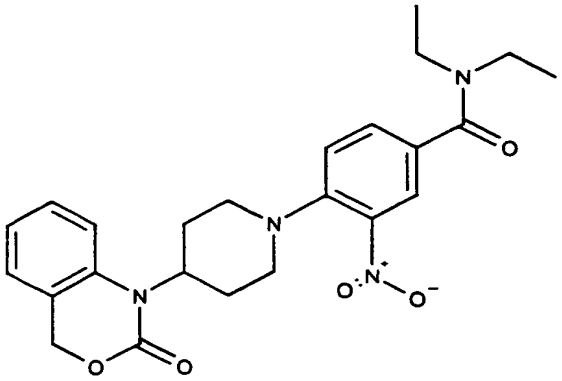
1-{1-[4-(Azepan-1-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 479(M+1)

Example 74

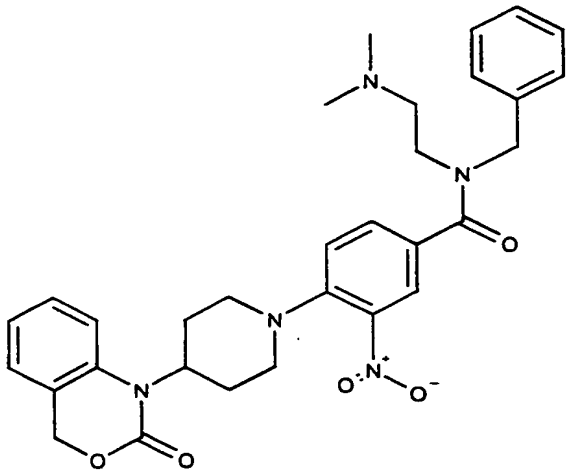
N,N-Diethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 453(M+1)

Example 75

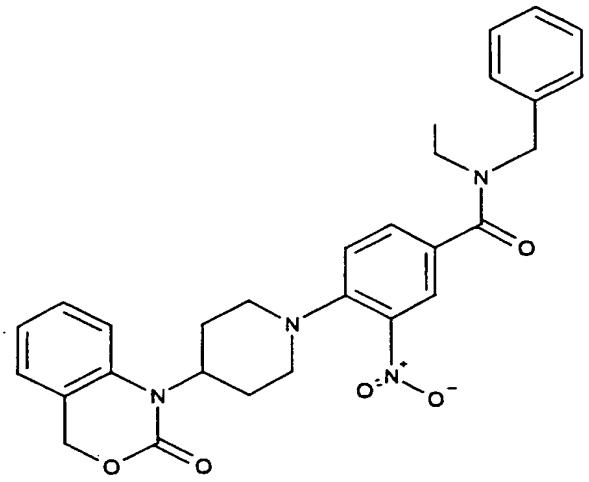
N-[2-(Dimethylamino)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide



MS: APCI(+ve) 558(M+1)

Example 76

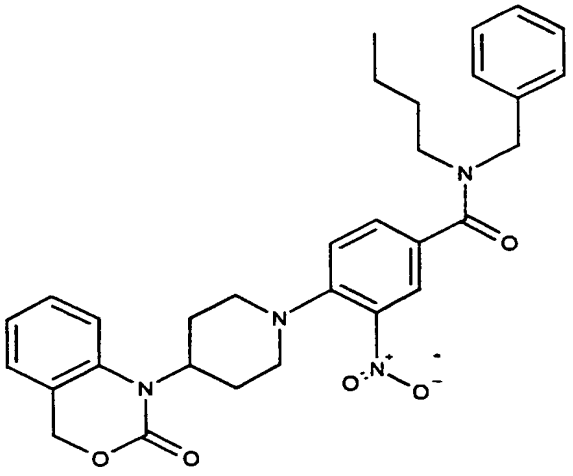
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide



MS: APCI(+ve) 515(M+1)

Example 77

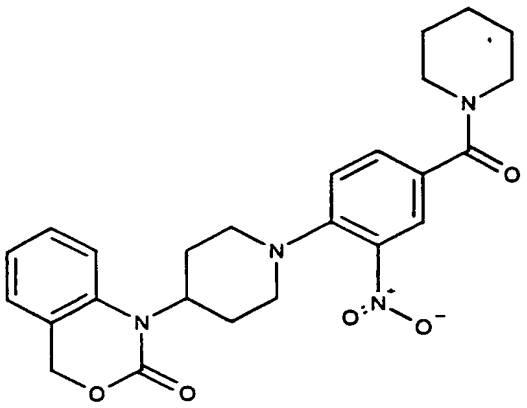
N-Butyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide



MS: APCI(+ve) 543(M+1)

Example 78

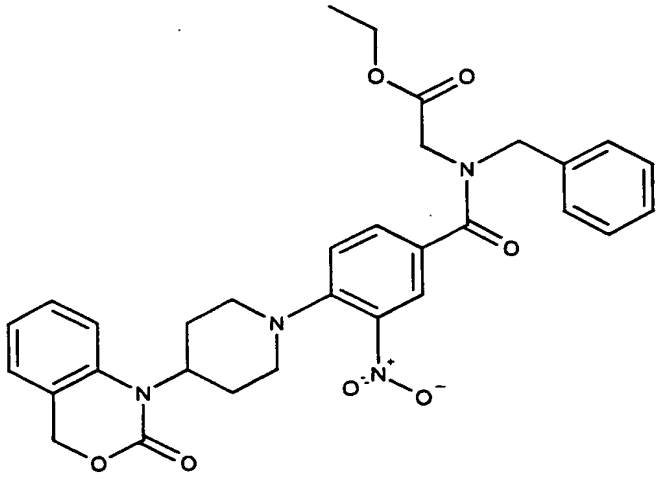
1-{1-[2-Nitro-4-(piperidin-1-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 465(M+1)

Example 79

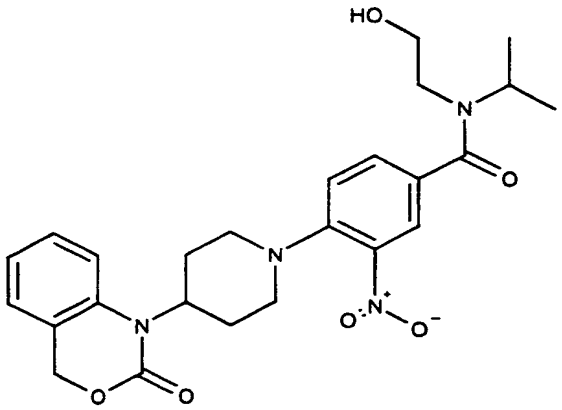
Ethyl [({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)(phenylmethyl)amino]acetate



MS: APCI(+ve) 573(M+1)

Example 80

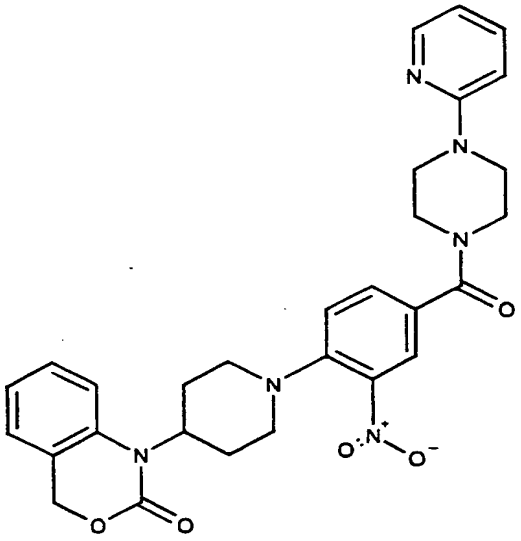
N-(2-Hydroxyethyl)-N-(1-methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 483(M+1)

Example 81

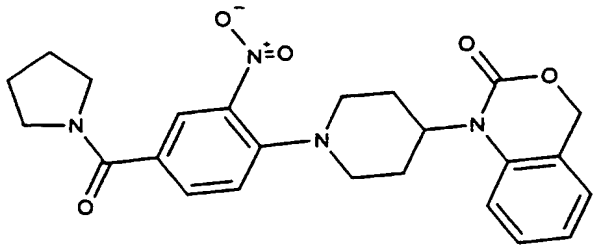
1-(1-{2-Nitro-4-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 543(M+1)

Example 82

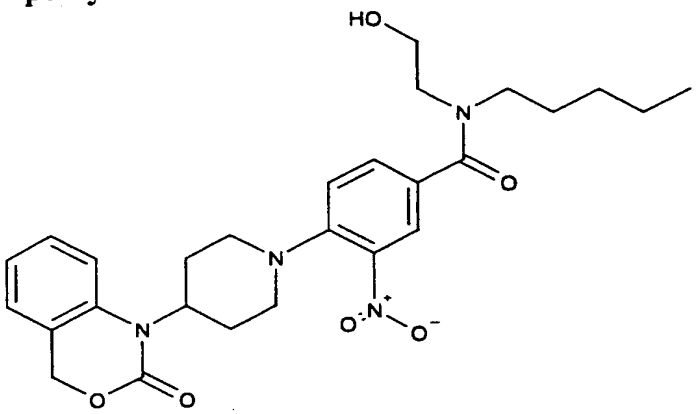
1-{1-[2-Nitro-4-(pyrrolidin-1-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 451(M+1)

Example 83

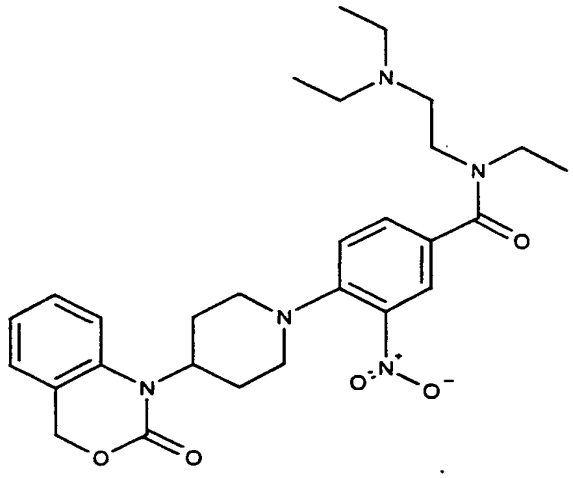
N-(2-Hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-pentylbenzamide



MS: APCI(+ve) 511(M+1)

Example 84

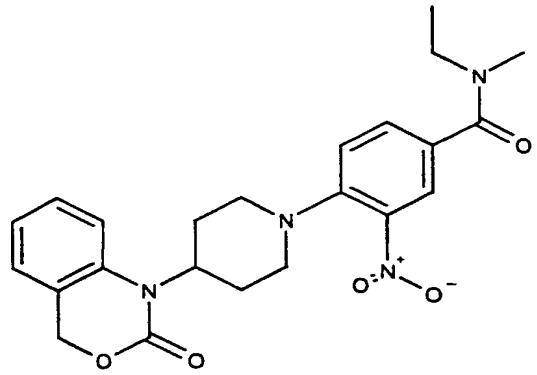
N-[2-(Diethylamino)ethyl]-N-ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 524(M+1)

Example 85

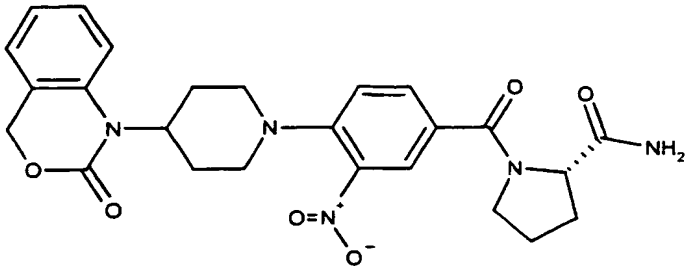
N-Ethyl-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 439(M+1)

Example 86

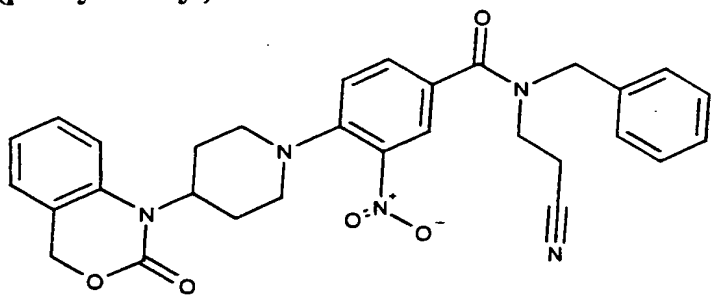
(2S)-1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)pyrrolidine-2-carboxamide



MS: APCI(+ve) 494(M+1)

Example 87

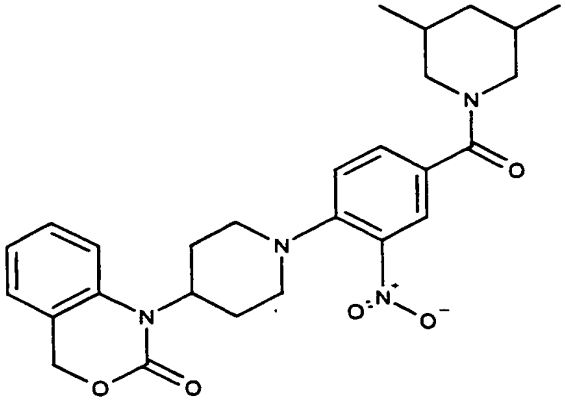
N-(2-Cyanoethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide



MS: APCI(+ve) 540(M+1)

Example 88

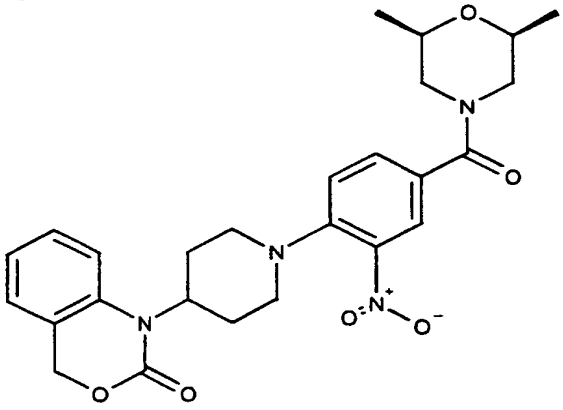
1-(1-{4-[(3,5-Dimethylpiperidin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 493(M+1)

Example 89

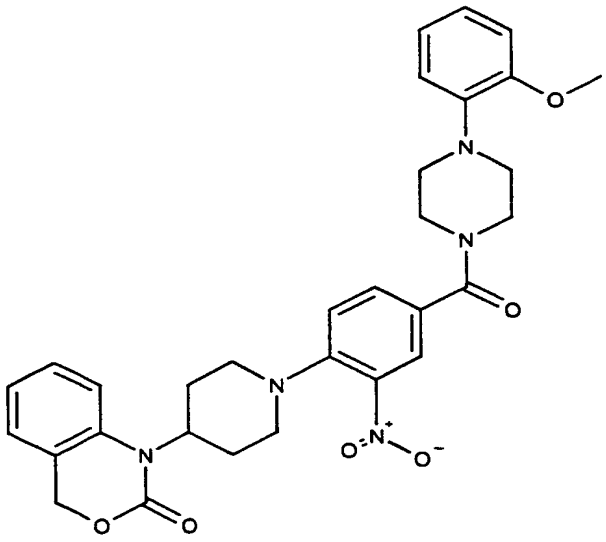
1-[1-(4-{[(2R,6S)-2,6-Dimethylmorpholin-4-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 495(M+1)

Example 90

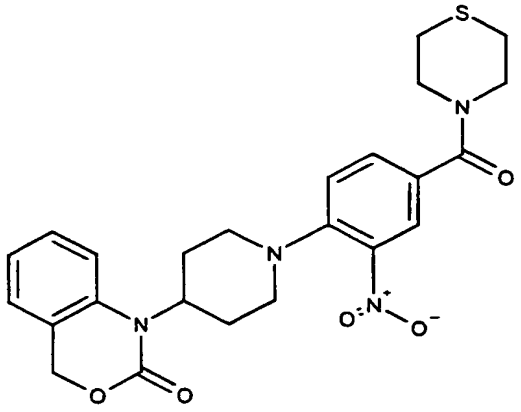
1-{1-[4-({4-[2-(Methyloxy)phenyl]piperazin-1-yl}carbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 572(M+1)

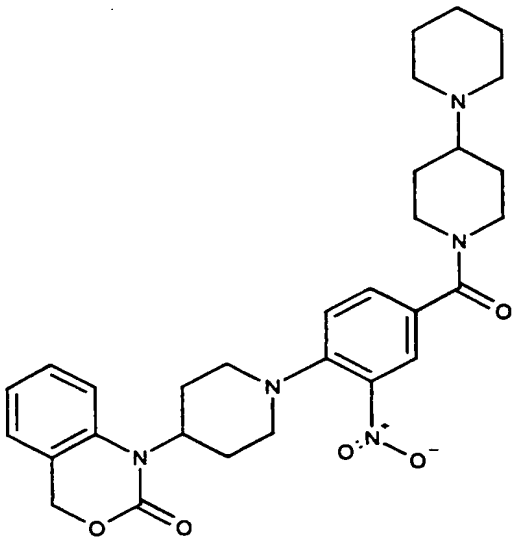
Example 91

1-{1-[2-Nitro-4-(thiomorpholin-4-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 483(M+1)

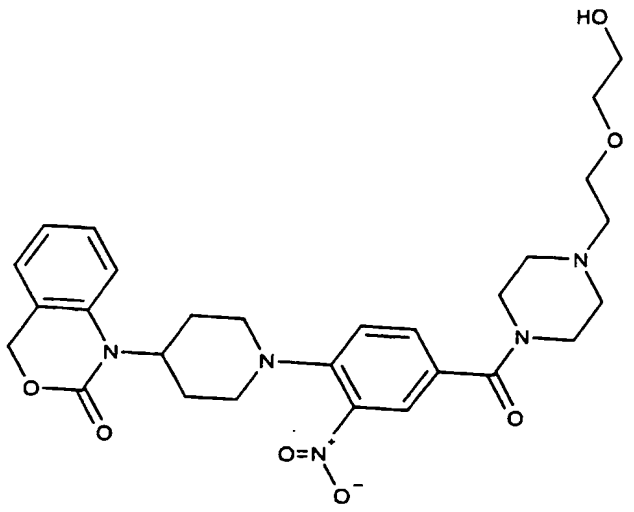
Example 92



MS: APCI(+ve) 548(M+1)

Example 93

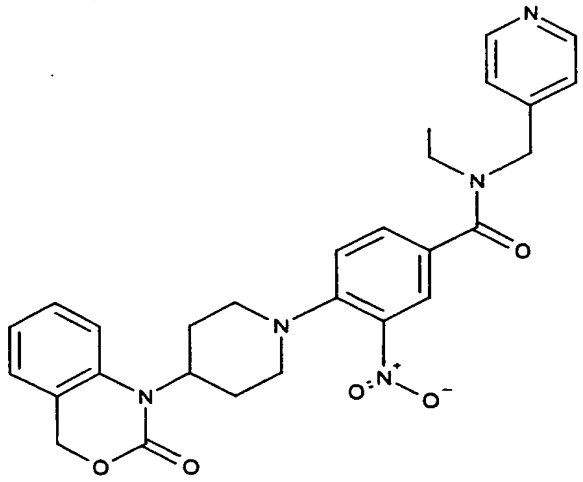
1-(1-{4-[(4-{2-[(2-Hydroxyethyl)oxy]ethyl}piperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 554(M+1)

Example 94

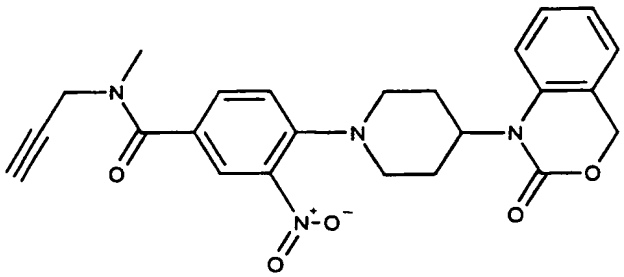
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(pyridin-4-ylmethyl)benzamide



MS: APCI(+ve) 516(M+1)

Example 95

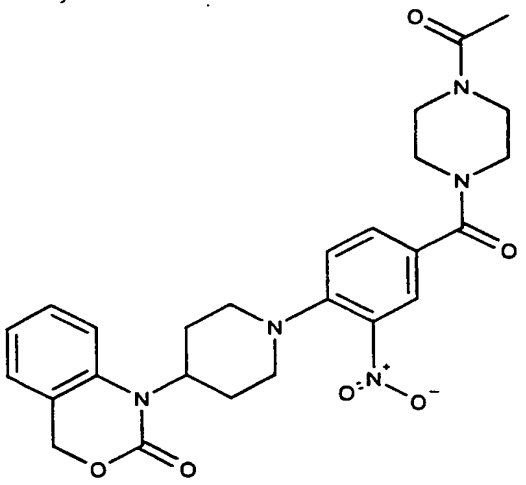
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-prop-2-ynylbenzamide



MS: APCI(+ve) 449(M+1)

Example 96

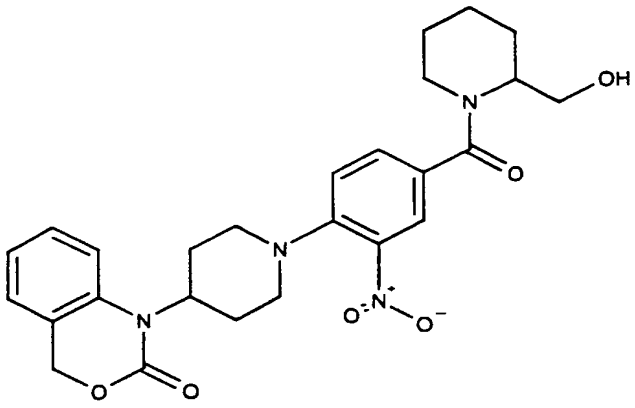
1-(1-{4-[(4-Acetylpiperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 508(M+1)

Example 97

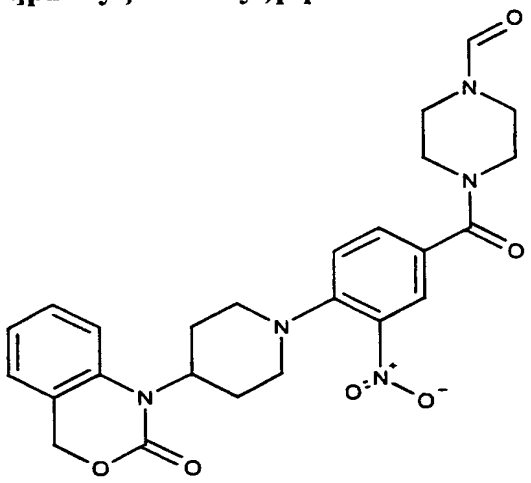
1-[1-(4-{[2-(Hydroxymethyl)piperidin-1-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 495(M+1)

Example 98

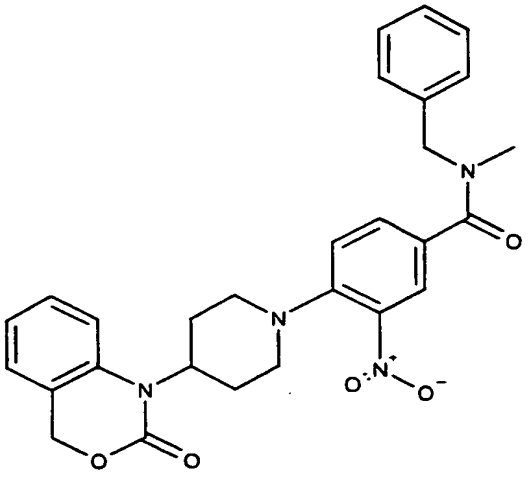
4-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazine-1-carbaldehyde



MS: APCI(+ve) 494(M+1)

Example 99

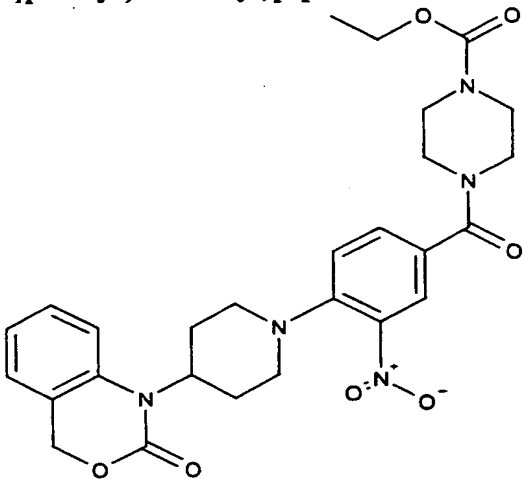
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide



MS: APCI(+ve) 501(M+1)

Example 100

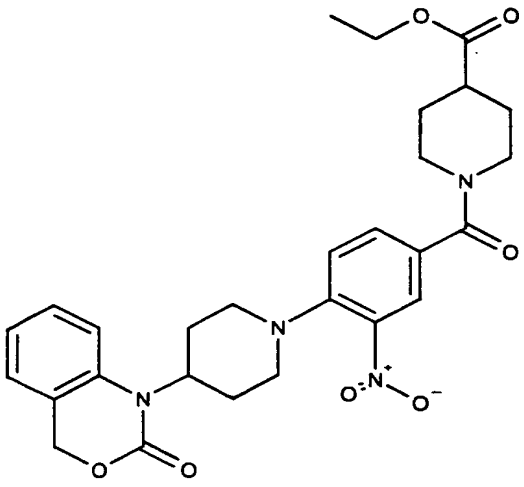
Ethyl 4-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazine-1-carboxylate



MS: APCI(+ve) 538(M+1)

Example 101

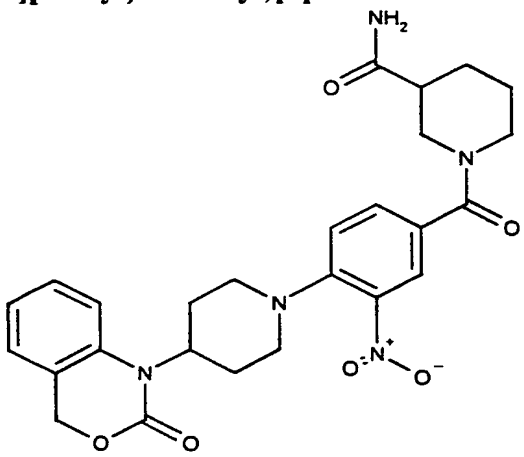
Ethyl 1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidine-4-carboxylate



MS: APCI(+ve) 537(M+1)

Example 102

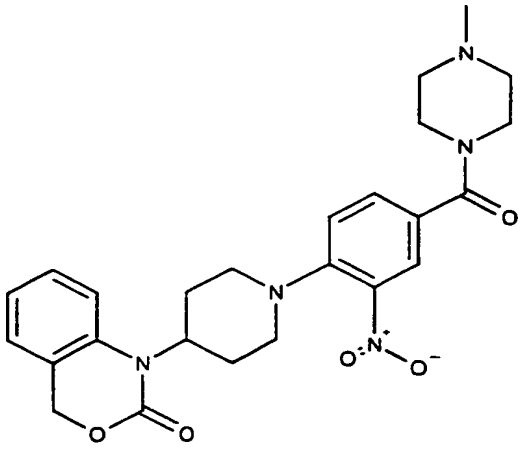
1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidine-3-carboxamide



MS: APCI(+ve) 508(M+1)

Example 103

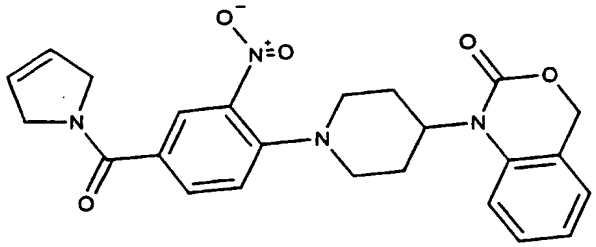
1-(1-{4-[(4-Methylpiperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 480(M+1)

Example 104

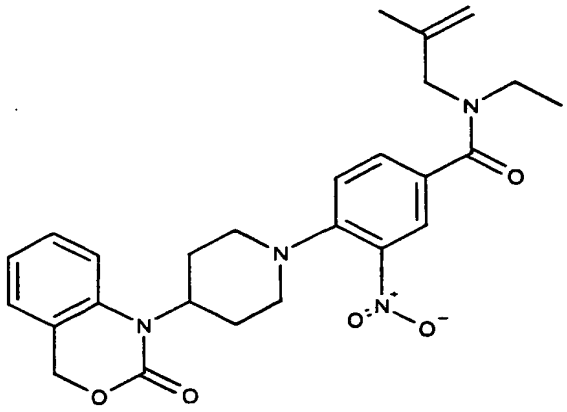
1-{1-[4-(2,5-Dihydro-1H-pyrrol-1-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 449(M+1)

Example 105

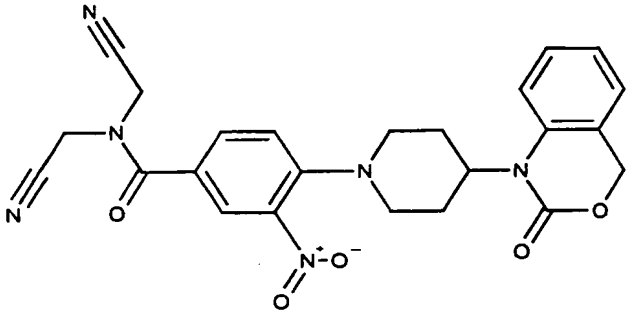
N-Ethyl-N-(2-methylprop-2-enyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 479(M+1)

Example 106

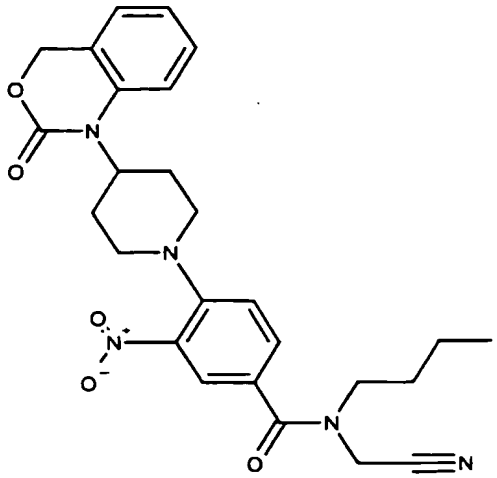
N,N-Bis(cyanomethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 475(M+1)

Example 107

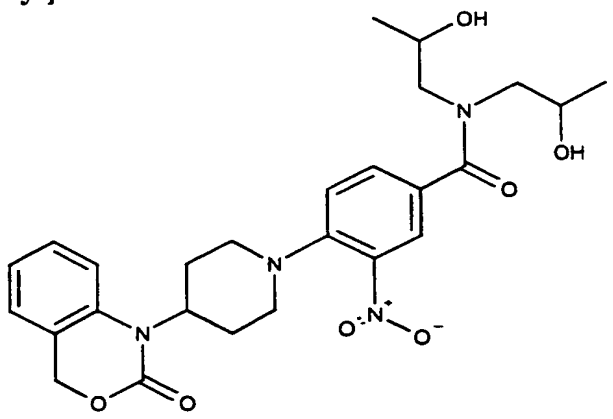
N-Butyl-N-(cyanomethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 492(M+1)

Example 108

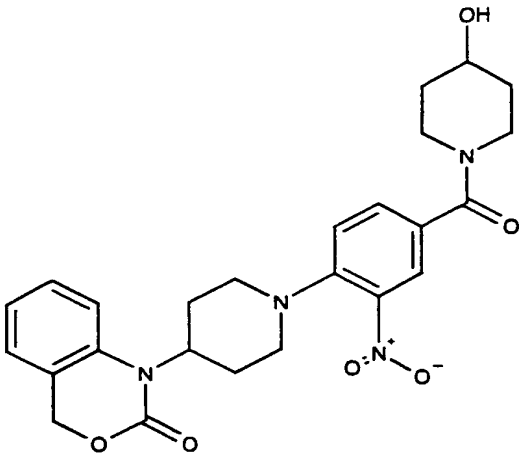
N,N-Bis(2-hydroxypropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 513(M+1)

Example 109

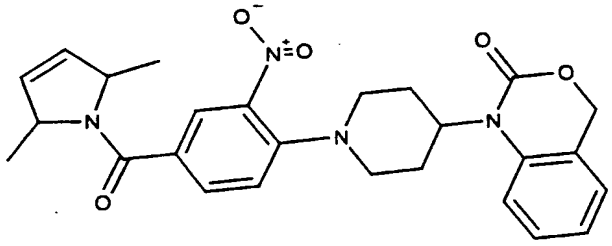
1-(1-{4-[(4-Hydroxypiperidin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 481(M+1)

Example 110

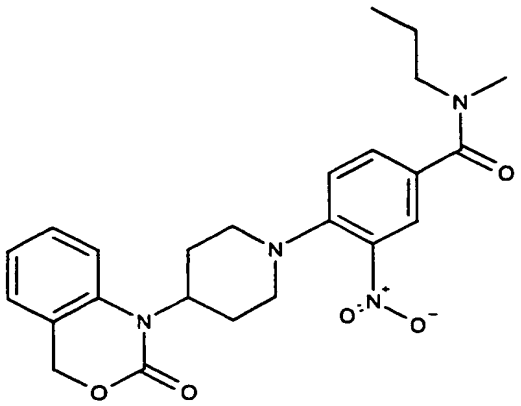
1-(1-{4-[(2,5-Dimethyl-2,5-dihydro-1H-pyrrol-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one



MS: APCI(+ve) 477(M+1)

Example 111

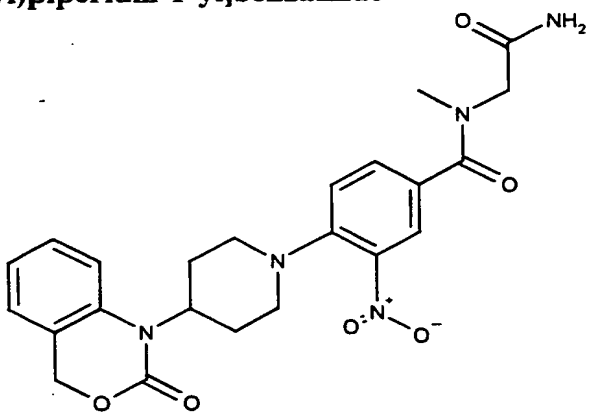
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-propylbenzamide



MS: APCI(+ve) 453(M+1)

Example 112

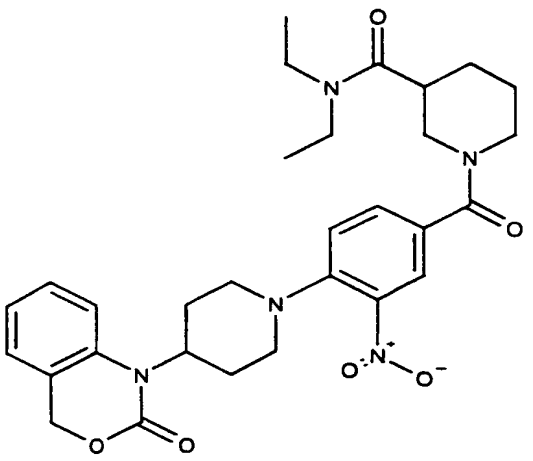
N-(2-Amino-2-oxoethyl)-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 468(M+1)

Example 113

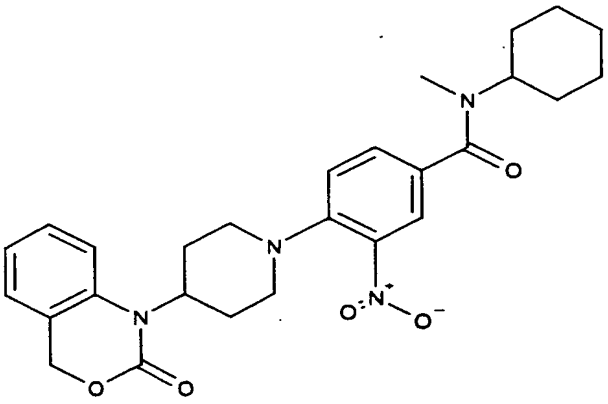
N,N-Diethyl-1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidine-3-carboxamide



MS: APCI(+ve) 564(M+1)

Example 114

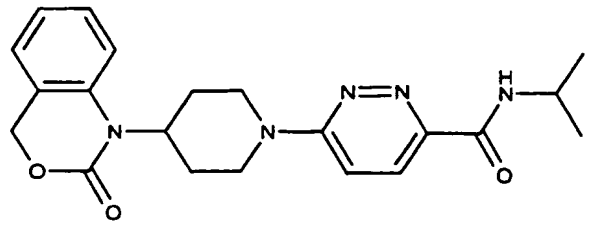
N-Cyclohexyl-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



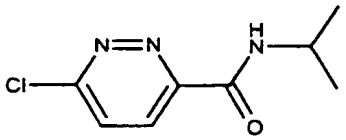
MS: APCI(+ve) 493(M+1)

Example 115

N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridazine-3-carboxamide



(i) 6-Chloro-N-(1-methylethyl)pyridazine-3-carboxamide



A solution of 6-chloro-3-pyridazinecarboxylic acid (0.25g) and carbonyldiimidazole (0.282g) in N,N-dimethylformamide (10ml) was stirred at room temperature for 1h. Isopropylamine (0.162ml) was added, the mixture stirred for 3h then partitioned between ethyl acetate and water. The organic layer was washed with water, dried, and evaporated under reduced pressure. Yield 0.284g.

1H NMR: δ (DMSO-d6) 9.02(1H, d), 8.22(1H, d), 8.09(1H, d), 4.22-4.13(1H, m), 1.21(6H, d)

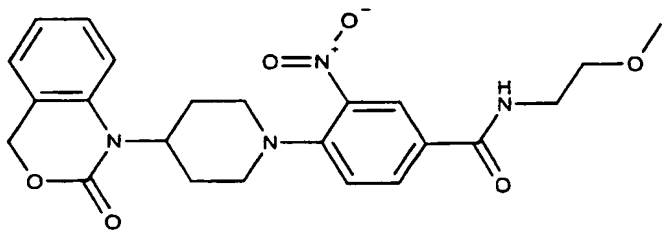
(ii) N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridazine-3-carboxamide

1-Piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.38g), the product from step (i) (0.28g) and N,N-diisopropylethylamine (0.73ml) in I-methyl-2-pyrrolidinone (6ml) was heated at 100°C for 8h. The mixture was partitioned between ethyl acetate and water, the organic layer washed with water, dried, and evaporated under reduced pressure. Purification was by chromatography eluting with 80% ethyl acetate/isohexane to yield 0.225g of a solid.

MS: APCI(+ve) 396(M+1)
1H NMR: δ (DMSO-d6) 8.51(1H, d), 7.84(1H, d), 7.45-7.35(3H, m), 7.30(1H, d), 7.13(1H, t), 5.14(2H, s), 4.64(2H, br d), 4.31-4.26(1H, m), 4.18-4.09(1H, m), 3.20(2H, t), 2.50-2.44(2H, m), 1.91(2H, br d), 1.19(6H, d)
MP:120°C

Example 116

N-[2-(Methyloxy)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

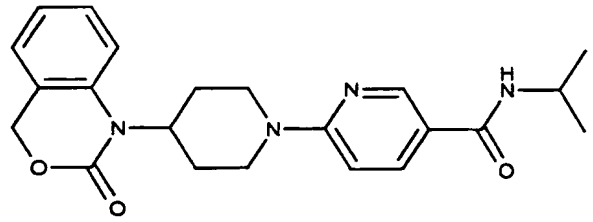


The title compound was prepared from the product of example 8 step (i) and 2-methoxyethylamine (0.5ml) using the method of example 115 step (i). Yield 0.065g.

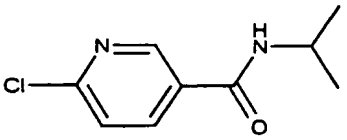
MS: APCI(+ve) 455(M+1)
1H NMR: δ ($CDCl_3$) 8.22(1H, dd), 7.92(1H, dd), 7.37(1H, t), 7.20-7.09(4H, m), 6.46(1H,br s), 5.10(2H, s), 4.25-4.17(1H, m), 3.68-3.47(6H, m), 3.40(3H, s), 3.15(2H, t), 2.93-2.79(2H, m), 1.95(2H, d)
MP:192-3°C

Example 117

N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide



(i) 6-Chloro-N-(1-methylethyl)pyridine-3-carboxamide



The product was prepared from 6-chloro-nicotinic acid (1.0g), carbonyldiimidazole (0.8g) and isopropylamine (0.6ml) using the method of example 115 step (i). Yield 0.75g.

MS: APCI(+ve) 199(M+1)

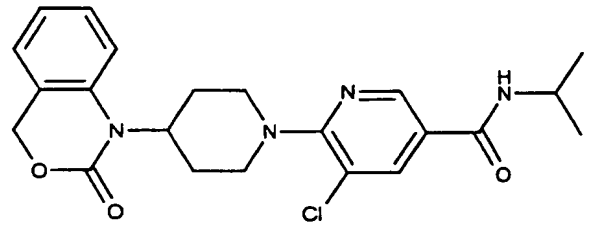
(ii) N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

The title compound was prepared from the product of step (i) (0.4g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.5g) using the method of example 115 step (ii). Yield 0.22g.

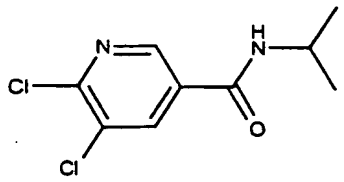
1H NMR: δ (DMSO-d6) 8.59(1H, d), 7.97-7.94(2H, m), 7.41-7.28(3H, m), 7.12(1H, t), 6.90(1H, d), 5.13(2H, s), 4.56(2H, br d), 4.25-4.18(1H, m), 4.12-4.00(1H, m), 3.06(2H, t), 2.50-2.38(2H, m), 1.85(2H, br d), 1.15(6H, d)
MP:>230°C

Example 118

5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide



(i) 5,6-Dichloro-N-(1-methylethyl)pyridine-3-carboxamide



The product was prepared from 5,6-dichloro-nicotinic acid (0.86g), carbonyldiimidazole (0.8g) and isopropylamine (0.52ml) using the method of example 115 step (i). Yield 0.69g.

MS: APCI(+ve) 199(M+1)

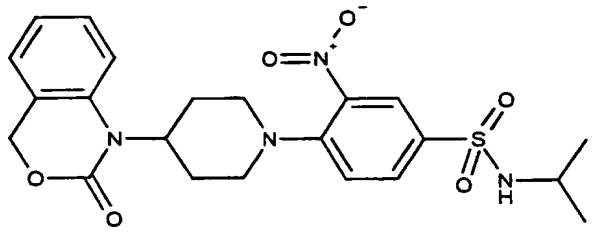
(ii) 5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

The title compound was prepared from the product of step (i) (0.3g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.35g) using the method of example 115 step (ii). Yield 0.187g.

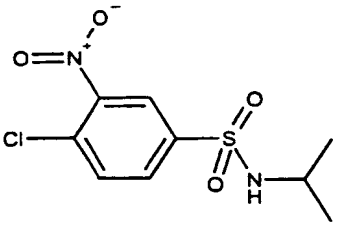
MS: APCI(+ve) 429(M+1)
1H NMR: δ (DMSO-d6) 8.64(1H, d), 8.25(1H, d), 8.18(1H, d), 7.40(1H, t), 7.33-7.30(2H, m), 7.12(1H, t), 5.15(2H, s), 4.18-4.02(4H, m), 3.06(2H, t), 2.71-2.60(2H, m), 1.89(2H, br d), 1.16(6H, d)
MP:216°C

Example 119

N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzenesulfonamide



(i) 4-Chloro-N-(1-methylethyl)-3-nitrobenzenesulfonamide



4-Chloro-3-nitrobenzenesulfonyl chloride (2g) and isopropylamine (2.1ml) in dichloromethane (30ml) was stirred at room temperature for 2h. The mixture was washed with water, 2M hydrochloric acid, water, dried and evaporated under reduced pressure. Yield 2.2g.

1H NMR: δ (DMSO-d6) 8.45(1H, d), 8.09-7.98(3H, m), 3.39-3.31(1H, septet), 0.99(6H, d)

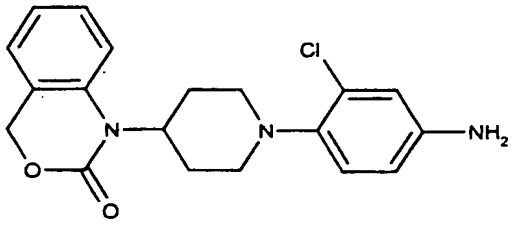
(ii) N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzenesulfonamide

The title compound was prepared from the product of step (i) (0.14g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.1g) using the method of example 115 step (ii). Yield 0.037g.

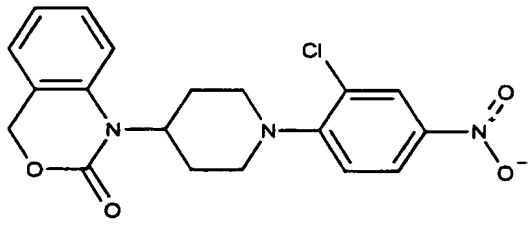
MS: APCI(+ve) 475(M+1)
1H NMR: δ (DMSO-d6) 8.17(1H, d), 7.86(1H, dd), 7.63(1H, d), 7.48(1H, d), 7.40(1H, t), 7.34-7.30(2H, m), 7.13(1H, t), 5.15(2H, s), 4.19-4.13(1H, m), 3.46(2H, d), 3.32-3.20(3H, m), 2.67-2.59(2H, m), 1.88(2H, d), 0.98(6H, d)
MP:168°C

Example120

1-[1-(4-Amino-2-chlorophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one



(i) 1-[1-(2-Chloro-4-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one



The product was prepared from 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (1.5g) and 3-chloro-4-fluoronitrobenzene (1.23g) using the method of example 115 step (ii). Yield 1.37g.

MS: APCI(+ve) 388(M+1)

(ii) 1-[1-(4-Amino-2-chlorophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one

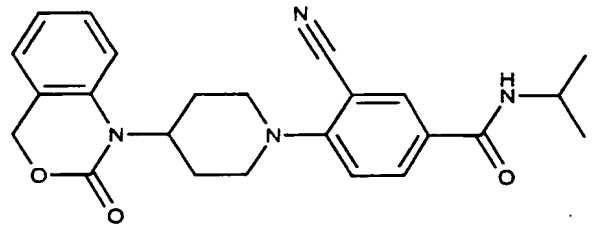
Iron powder (1.5g) was added to a solution of the product from step (i) (1.37g) in acetic acid (50ml) and tetrahydrofuran (20ml). After stirring at room temperature for 5h, the mixture was filtered through celite, the solvent removed under reduced pressure and the

residue partitioned between ethyl acetate and aqueous sodium hydrogencarbonate solution. The organic layer was washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 50% ethyl acetate/isohexane. Yield 1.05g.

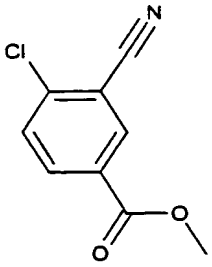
MS: APCI(+ve) 358(M+1)
1H NMR: δ (DMSO-d6) 7.40(1H, t), 7.29(2H, m), 7.12(1H, t), 6.92(1H, d), 6.64(1H, d), 6.49(1H, dd), 5.14(2H, s), 5.03(2H, s), 3.98-3.92(1H, m), 3.14(2H, d), 2.77-2.62(4H, m), 1.83(2H, br d)
MP:158°C

Example 121

3-Cyano-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



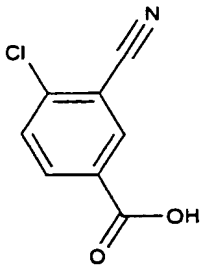
(i) Methyl 4-chloro-3-cyanobenzoate



A solution of sodium nitrite (1.28g) in water (8ml) was added over 10min to a mixture of methyl 3-amino-4-chlorobenzoate (4.0g) in water (40ml) and concentrated hydrochloric acid (5ml) at 0°C. After 30min the mixture was neutralised with aqueous sodium hydroxide solution to pH~7 then added portionwise to a solution of copper cyanide (prepared from sodium cyanide (2.87g) and copper(I) chloride (2.23g) in water (40ml)) at 0°C. The mixture was stirred at room temperature for 2h then partitioned between ethyl acetate and water. The organics were washed with water, dried and evaporated under reduced pressure. The residue was triturated with 20% ethyl acetate/isohexane to yield a solid (1.55g).

1H NMR: δ ($CDCl_3$) 8.34(1H, d), 8.21-8.17(1H, m), 7.62(1H, dd), 3.96(3H, s)

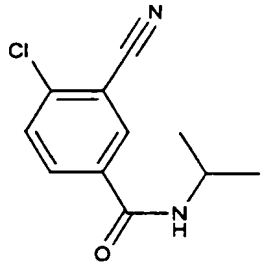
(ii) 4-Chloro-3-cyanobenzoic acid



A solution of the product from step (i) (1.5g) and lithium hydroxide hydrate (0.84g) in a mixture of (1:1)water and tetrahydrofuran (40ml) was stirred at room temperature for 2h. The tetrahydrofuran was removed under reduced pressure and the residue partitioned between diethyl ether and water. The aqueous layer was acidified with 2M hydrochloric acid then extracted with ethyl acetate. The organic layer was dried and evaporated under reduced pressure. Yield 1.3g.

1H NMR: δ ($CDCl_3$) 8.42(1H, d), 8.28-8.24(1H, m), 7.67(1H, dd)

(iii) 4-Chloro-3-cyano-N-(1-methylethyl)benzamide



The above compound was prepared from the product of step (ii) (0.6g), carbonyldiimidazole (0.59g) and isopropylamine (0.51ml) using the method of example 115 step (i). Yield 0.68g.

1H NMR: δ ($CDCl_3$) 8.06(1H, d), 7.96-7.92(1H, m), 7.59(1H, d), 5.96(1H, br s), 4.28(1H, septet), 1.29(6H, d)

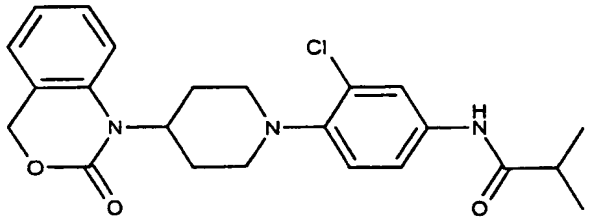
(iv) 3-Cyano-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

The title compound was prepared from the product of step (iii) (0.29g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.3g) using the method of example 115 step (ii). Yield 0.073g.

MS: APCI(+ve) 419(M+1)
1H NMR: δ (DMSO-d6) 8.21(1H, d), 8.18(1H, d), 8.03(1H, dd), 7.40(1H, t), 7.34-7.30(2H, m), 7.22(1H, d), 7.13(1H, t), 5.16(2H, s), 4.16-4.04(2H, m), 3.81(2H, br d), 3.14(2H, t), 2.75-2.65(2H, m), 1.93(2H, br d), 1.16(6H, d)
MP:200°C

Example 122

N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-2-methylpropanamide

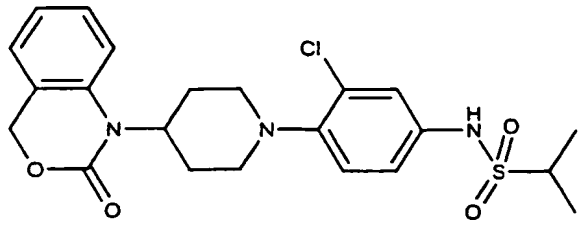


Isobutyryl chloride (0.017ml) was added to a stirred solution of the product from example 120 step (ii) (0.05g) and triethylamine (0.07ml) in dichloromethane (1ml) at room temperature. After 2h the mixture was partitioned between ethyl acetate and water, the organics separated, washed with water, dried, and evaporated under reduced pressure. Trituration with ether gave a solid, yield 0.048g.

MS: APCI(+ve) 428(M+1)
1H NMR: δ (DMSO-d6) 9.86(1H, s), 7.79(1H, d), 7.46(1H, dd), 7.42-7.38(1H, m), 7.31-7.29(2H, m), 7.14-7.10(2H, m), 5.15(2H, s), 4.04-3.98(1H, m), 3.33-2.84(2H, m), 2.82(2H, t), 2.75-2.65(2H, m), 2.59-2.50(1H, m), 1.87(2H, br d), 1.09(6H, d)
MP:228°C

Example 123

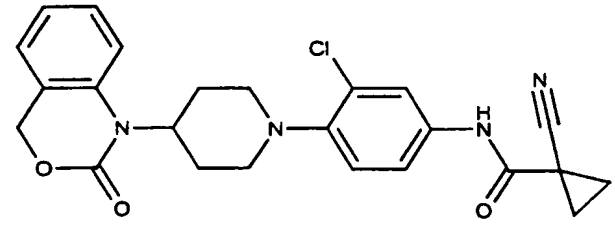
N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}propane-2-sulfonamide



Isopropylsulphonyl chloride (0.03ml) was added to a stirred solution of the product from example 120 step (ii) (0.05g), pyridine (0.1ml) in acetonitrile (0.9ml) at room temperature. The mixture was stirred overnight, partitioned between ethyl acetate and water, the organics separated, washed with water, dried, and evaporated under reduced pressure. Purification was by chromatography eluting with 40% ethyl acetate/isohexane. Yield 0.015g.

MS: APCI(+ve) 464(M+1)
1H NMR: δ (DMSO-d6) 9.76(1H, s), 7.40(1H, t), 7.31-7.27(3H, m), 7.19-7.10(3H, m), 5.15(2H, s), 4.04-3.98(1H, m), 3.30(2H, br d), 3.25-3.18(1H, m), 2.82(2H, t), 2.74-2.65(2H, m), 1.87(2H, br d), 1.24(6H, d)
MP:175°C

Example 124
N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-1-cyanocyclopropanecarboxamide

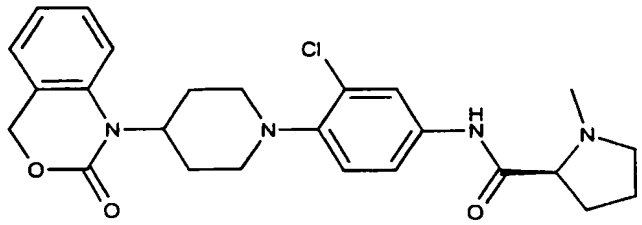


The title compound was prepared from the product of example 120 step (ii) (0.05g), carbonyldiimidazole (0.025g) and 1-cyano-1-cyclopropane carboxylic acid (0.019g) using the method of example 115 step (i). Yield 0.003g.

MS: APCI(+ve) 451(M+1)
1H NMR: δ (DMSO-d6) 10.02(1H, s), 7.70(1H, d), 7.52-7.48(1H, m), 7.40(1H, t), 7.30(2H, t), 7.17-7.10(2H, m), 5.15(2H, s), 4.05-3.99(1H, m), 3.32(2H, d), 2.83(2H, t), 2.74-2.67(2H, m), 1.88(2H, d), 1.67(4H, s)

Example 125

(2S)-N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-1-methylpyrrolidine-2-carboxamide



A mixture of the product from example 120 step (ii) (0.1g), N-methyl-L-proline (0.044g), N,N-diisopropylethylamine (0.17ml), 1-hydroxybenzotriazole (0.043g), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.103g) in N,N-dimethylformamide (3ml) were stirred at room temperature overnight then partitioned between ethyl acetate and water. The organic layer was washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 4% methanol/dichloromethane. Yield 0.038g.

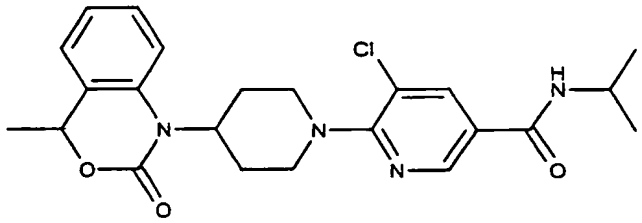
MS: APCI(+ve) 469(M+1)

1H NMR: δ (DMSO-d6) 9.73(1H, s), 7.88(1H, d), 7.59(1H, dd), 7.38(1H, t), 7.30(2H, d), 7.14-7.10(2H, m), 5.15(2H, s), 4.04-3.98(1H, m), 3.30(2H, d), 3.12-3.08(1H, m), 2.90-2.67(5H, m), 2.35-2.29(1H, m), 2.33(3H, s), 2.18-2.09(1H, m) 1.87(2H, br d), 1.82-1.75(3H, m)

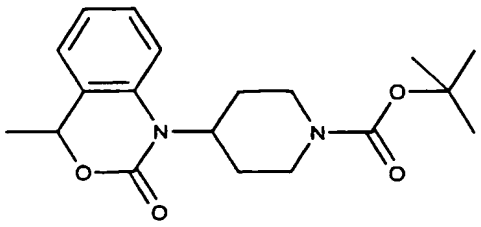
MP:155°C

Example 126

5-Chloro-N-(1-methylethyl)-6-[4-(4-methyl-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide



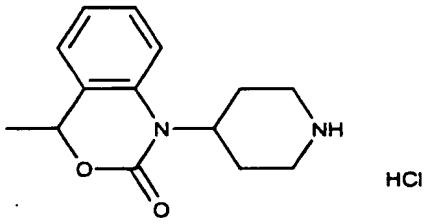
(i) 1,1-Dimethylethyl 4-(4-methyl-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate



Acetic acid (1ml) was added dropwise to a solution of N-tert-butoxycarbonyl-4-piperidone (9.4g), 1-(2-amino-phenyl)-ethanol (4.3g) and sodium cyanoborohydride (10g) in dichloromethane and the mixture stirred at room temperature overnight. The mixture was partitioned between ethyl acetate and water, the organics separated and washed with aqueous sodium hydrogencarbonate solution, water, dried, and evaporated under reduced pressure. The crude product was dissolved in tetrahydrofuran (100ml) and N,N-diisopropylethylamine (23ml), cooled to 0°C, then triphosgene (4.3g) added. The mixture was warmed to room temperature and stirred overnight. The mixture was partitioned between ethyl acetate and water, the organics washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 20% ethyl acetate/isohexane. Yield 1.4g.

MS: APCI(+ve) 247(M+1-Boc)

(ii) 4-Methyl-1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride



4M Hydrogen chloride in 1,4-dioxane (20ml) was added to a solution of the product from step (i) (1.4g) in 1,4-dioxane (20ml) and the mixture stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue triturated with ether. Yield 1.0g.

MS: APCI(+ve) 247(M+1)

(iii) 5-Chloro-N-(1-methylethyl)-6-[4-(4-methyl-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

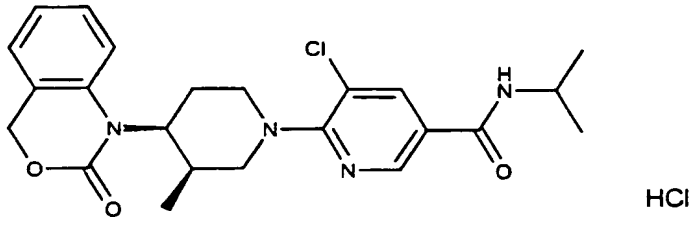
The title compound was prepared from the product of step (ii) (0.36g) and the product from example 117 step (i) (0.466g) using the method of example 115 step (ii). Yield 0.112g

MS: APCI(+ve) 443(M+1)

1H NMR: δ (DMSO-d6) 8.64(1H, d), 8.25(1H, d), 8.18(1H, d), 7.42-7.38(1H, m), 7.34-7.27(2H, m), 7.16-7.12(1H, m), 5.36(1H, q), 4.18-4.05(4H, m), 3.09-3.02(2H, m), 2.72-2.61(2H, m), 1.89(2H, br d), 1.57(3H,d), 1.16(6H, d)

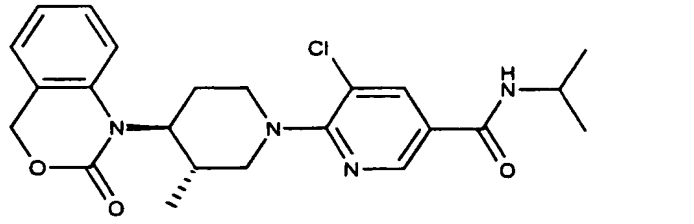
Examples 127

±-5-Chloro-N-(1-methylethyl)-6-[(cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide hydrochloride

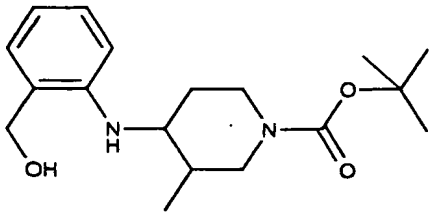


Example 128

±-5-Chloro-N-(1-methylethyl)-6-[(trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide hydrochloride



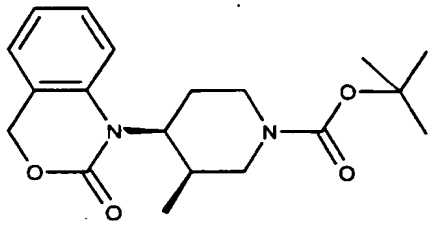
(i) 1,1-Dimethylethyl 4-{[2-(hydroxymethyl)phenyl]amino}-3-methylpiperidine-1-carboxylate

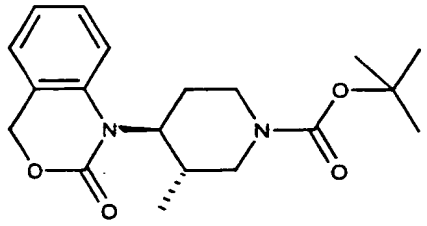


The product was prepared from N-tert-butoxycarbonyl-3-methyl-4-piperidone (4.3g) and 2-amino-benzyl alcohol (2.59g) using the method of example 7 step (i). Yield 6.3g as a mixture of diastereoisomers.

MS: APCI(+ve) 320(M+1)

(ii) ±-1,1-Dimethylethyl (cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate
±-1,1-Dimethylethyl (trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate





The above compounds were prepared from the product of step (i) (6.3g) using the method of example 7 step (ii). Cis and trans diastereoisomers were separated (relative stereochemistry).

±-1,1-Dimethylethyl (cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate, yield 0.24g MS: APCI(+ve) 247(M+1)

±-1,1-Dimethylethyl (trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate, yield 0.68g MS: APCI(+ve) 247(M+1)

(iii) ±-5-Chloro-N-(1-methylethyl)-6-[(cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide hydrochloride

±-1,1-Dimethylethyl (cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate (0.24g) was dissolved in 4M hydrogen chloride in 1,4-dioxane (5ml) stirred at room temperature for 4h, then evaporated under reduced pressure. The product was dissolved in 1-methyl 2-pyrrolidinone (10ml), N,N-diisopropylethylamine (0.5ml) and the product from example 117 step (i) (0.23g) added. The mixture was heated at 100°C for 12h, partitioned between ethyl acetate and water , the organics separated, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 30-

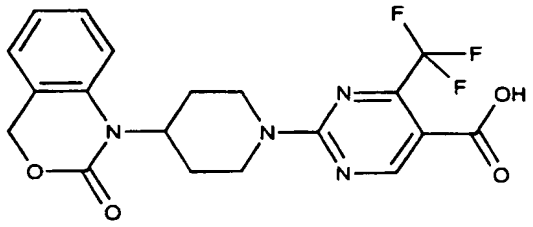
40% ethyl acetate/isohexane. The hydrochloride salt was made from ethereal hydrogen chloride. Yield 0.07g.

MS: APCI(+ve) 443(M+1)
1H NMR: δ (DMSO-d6) 8.64(1H, d), 8.27(1H, d), 8.19(1H, d), 7.41-7.30(3H, m), 7.12(1H, t), 6.12(2H, br s), 5.22-5.14(2H, m), 4.12-3.99(3H, m), 3.77(1H, br s), 3.13(1H, br t), 2.86(1H, br s), 2.75-2.50(2H, m), 1.94(1H, br d), 1.16(6H, d), 0.87(3H, d)
MP:215°C

±-5-chloro-N-(1-methylethyl)-6-[(trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide hydrochloride
The titled compound was prepared from ±-1,1-dimethylethyl (trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate (0.68g) using the same method as step (iii). Yield 0.219g.

MS: APCI(+ve) 443(M+1)
1H NMR: δ (DMSO-d6) 8.63(1H, s), 8.25(1H, d), 8.17(1H, s), 7.40-7.29(2H, m), 7.28(1H, d), 7.12(1H, t), 6.04(2H, br s), 5.21-5.13(2H, m), 4.29-4.24(1H, m), 4.12-3.91(3H, m), 3.30(1H, dd), 3.18-3.02(2H, m), 2.56-2.54(1H, m), 1.87(1H, br d), 1.16(6H, d), 1.09(3H, d)
MP:195°C

Examples 129-144
(i) 2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxylic acid



The title compound was prepared from 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.70g) and 2-chloro-4-(trifluoromethyl)pyrimidine-5-carboxylic acid (1.8g) using the method of example 115 step (ii). Yield 1.1g.

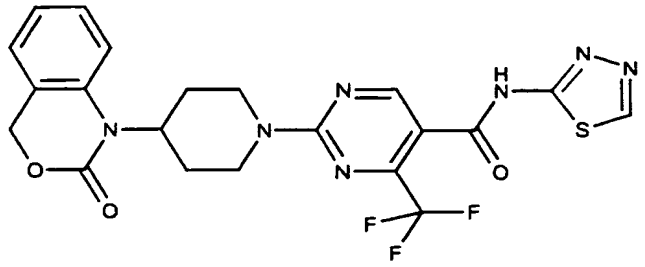
MS: APCI(+ve) 423(M+1)

(ii) Examples 129-144

Oxalyl chloride (0.1ul) was added to a solution of the product from step (i) (0.27g) in dichloromethane (10ml) and stirred at room temperature for 3h. The solvent was removed under reduced pressure and the residue dissolved in 1-methyl-2-pyrrolidinone. An aliquot of the solution of the acid chloride (0.1ml), the appropriate amine (2 equivalents) and triethylamine (5 equivalents) in 1-methyl-2-pyrrolidinone (0.03ml) were left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

Example 129

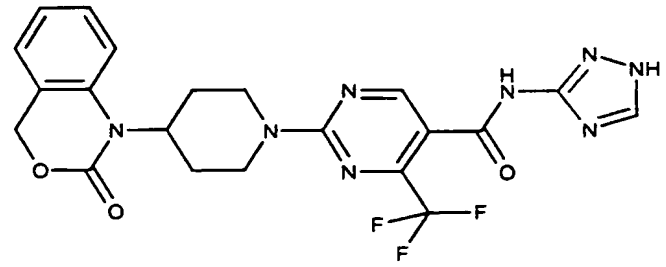
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1,3,4-thiadiazol-2-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 505(M+1)

Example 130

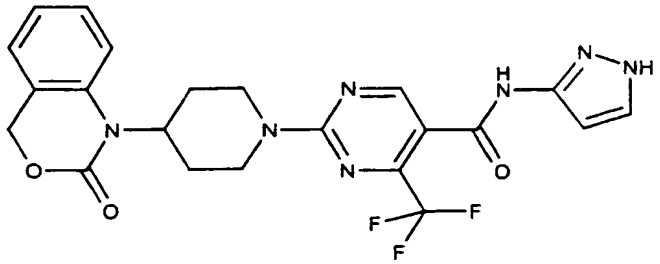
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 488(M+1)

Example 131

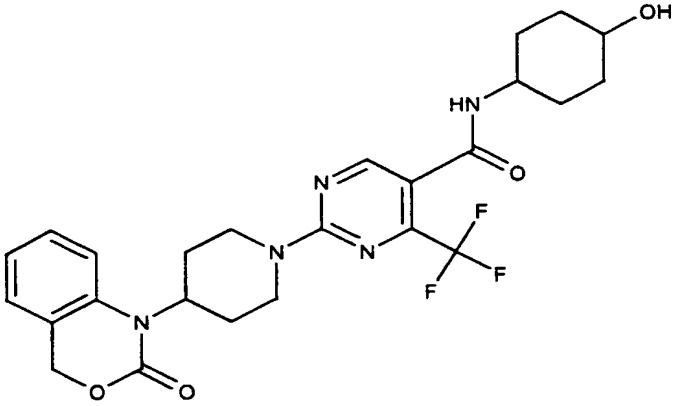
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1H-pyrazol-3-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 487(M+1)

Example 132

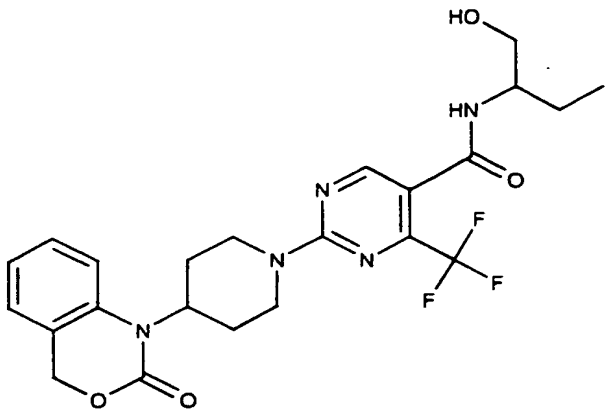
N-(4-Hydroxycyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 519(M+1)

Example 133

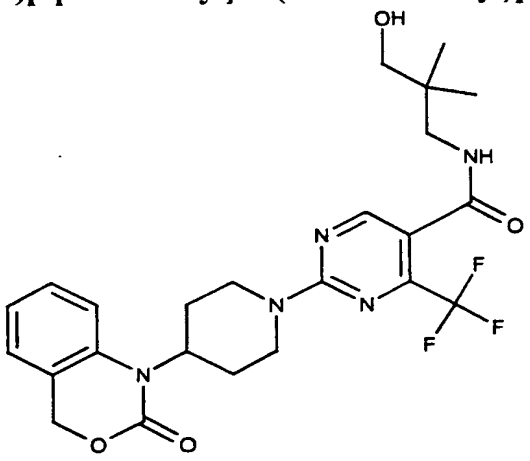
N-[1-(Hydroxymethyl)propyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 493(M+1)

Example 134

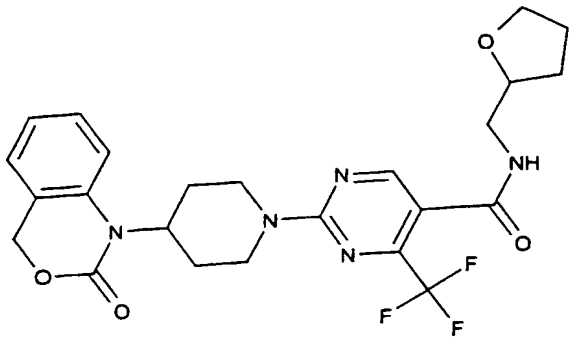
N-(3-Hydroxy-2,2-dimethylpropyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 507 (M+1)

Example 135

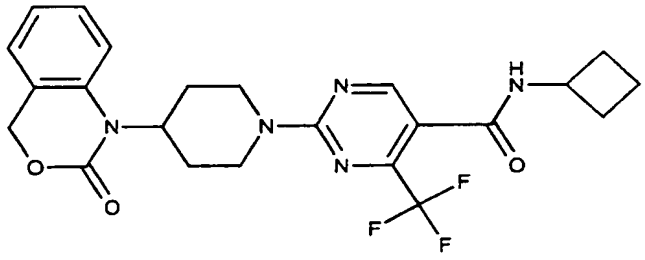
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(tetrahydrofuran-2-ylmethyl)-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 505(M+1)

Example 136

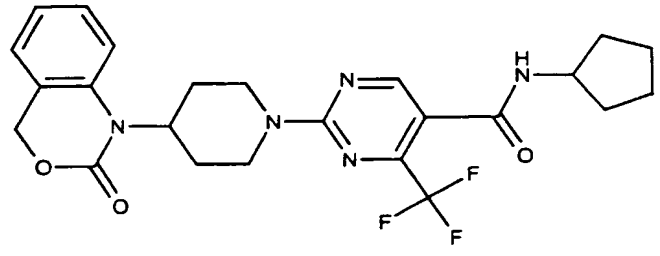
N-Cyclobutyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 475(M+1)

Example 137

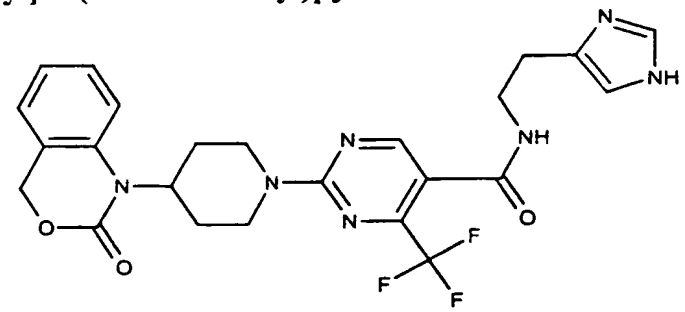
N-Cyclopentyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 489(M+1)

Example 138

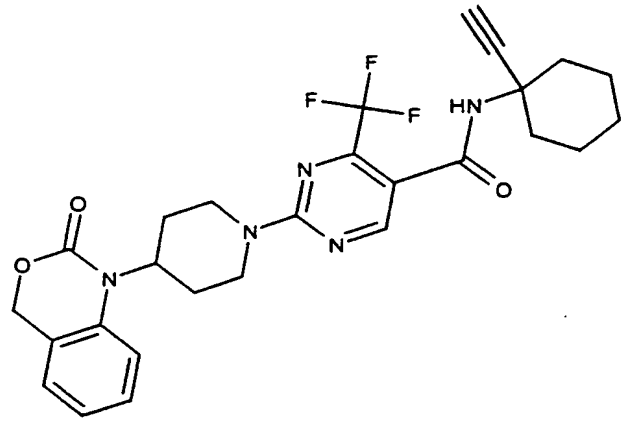
N-[2-(1H-Imidazol-4-yl)ethyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 515(M+1)

Example 139

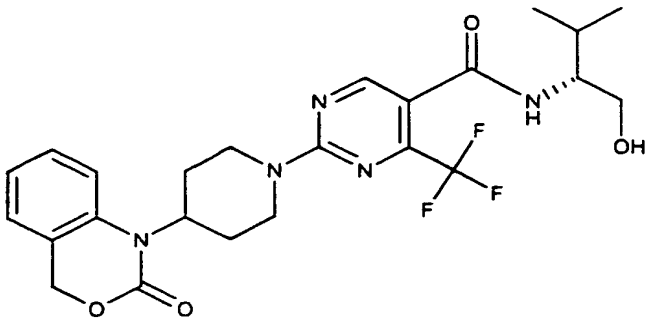
N-(1-Ethynylcyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 527(M+1)

Example 140

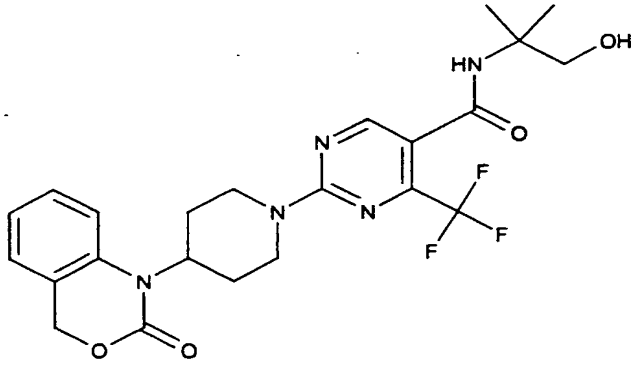
N-[(1R)-1-(Hydroxymethyl)-2-methylpropyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 507(M+1)

Example 141

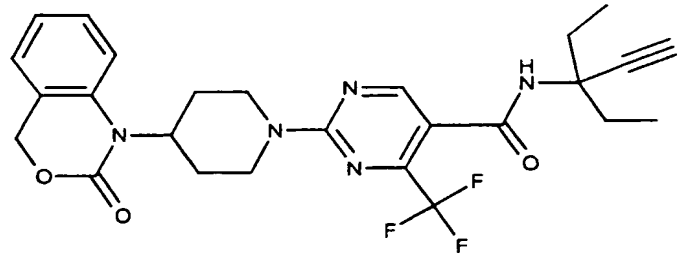
N-(2-Hydroxy-1,1-dimethylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 493(M+1)

Example 142

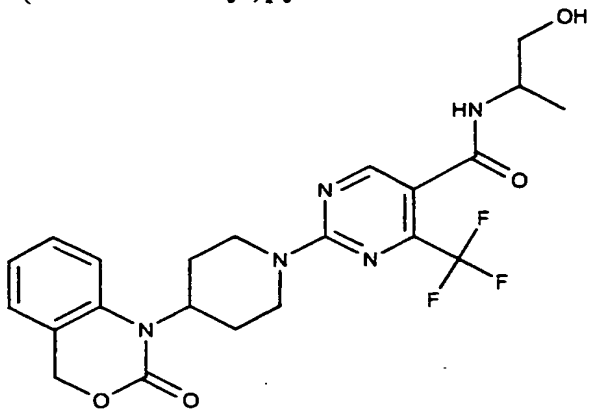
N-(1,1-Diethylprop-2-ynyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 515(M+1)

Example 143

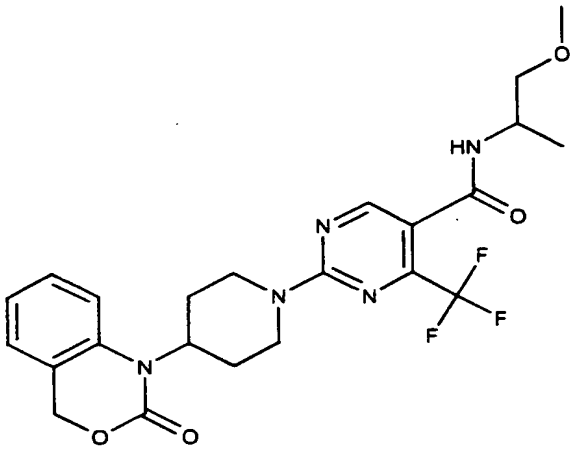
N-(2-Hydroxy-1-methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



MS: APCI(+ve) 479(M+1)

Example 144

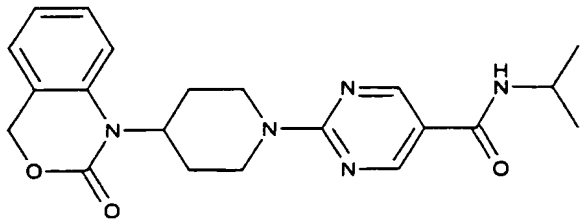
N-[1-Methyl-2-(methyloxy)ethyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide



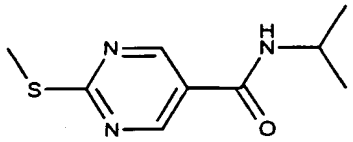
MS: APCI(+ve) 493(M+1)

Example 145

N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyrimidine-5-carboxamide



(i) N-(1-Methylethyl)-2-(methylthio)pyrimidine-5-carboxamide



The product was prepared from N-(1-methylethyl)-2-(methylthio)pyrimidine-5-carboxylic acid (Acta Chem Scand., Ser.B (1986), B40(9), 764-767.) (0.78g), carbonyldiimidazole (0.82g) and isopropylamine (0.3g) using the method of example 115 step (i). Yield 0.66g.

MS: APCI(+ve) 212 (M+1)

(ii) N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyrimidine-5-carboxamide

The product from step (i) (0.66g) was dissolved in chloroform (50ml) and to this solution was added 3-chloroperoxybenzoic acid (2.02g). The mixture was stirred for 1h at room temperature before being washed with an aqueous solution of sodium metabisulphite followed by aqueous sodium bicarbonate. The organic layer was dried and evaporated under reduced pressure. The residue was dissolved in 1-methyl-2-pyrrolidinone (4ml) and this solution treated with *N,N* –diisopropylethylamine (0.5ml) followed by 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.2g) before being heated at 60°C for 2h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with ethyl acetate/isohexane (2/1). Yield 0.03g as a solid.

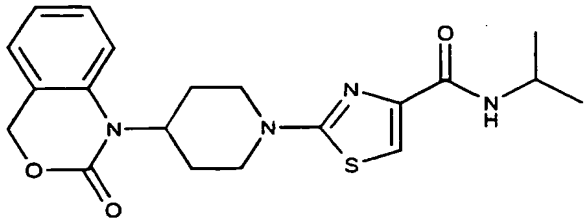
MS: APCI(+ve) 396 (M+1)

1H NMR: δ (DMSO-d6) 8.77(2H, s), 8.07(1H, d), 7.41-7.29(3H, m), 7.12(1H, t), 5.14(2H, s), 4.88(2H, d), 4.28-4.22(1H, m), 4.11-4.02(1H, m), 3.12(2H, t), 2.45-2.33(2H, m), 1.89(2H, d), 1.16(6H, d)

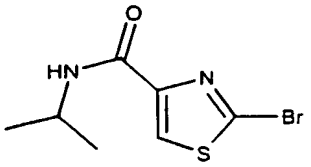
MP:236-239°C

Example 146

N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-1,3-thiazole-4-carboxamide



(i) 2-Bromo-N-(1-methylethyl)-1,3-thiazole-4-carboxamide



The product was prepared from 2-bromo-N-(1-methylethyl)-1,3-thiazole-4-carboxylic acid (WO 9848799) (0.77g), carbonyldiimidazole (0.66g) and isopropylamine (0.24g) using the method of example 115 step (i). Yield 0.82g.

1H NMR: δ (DMSO-d6) 8.25(1H, s), 8.24-8.18(1H, m), 4.14-4.02(1H, m), 1.16(6H, d)

(ii) N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-1,3-thiazole-4-carboxamide

The title compound was prepared from the product of step (i) (0.16g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.15g) using the method of example 115 step (ii). Yield 0.04g.

MS: APCI(+ve) 401 (M+1)

1H NMR: δ (DMSO-d6) 7.68(1H, d), 7.43-7.29(4H, m), 7.13(1H, t), 5.16(2H, s), 4.22-3.99(4H, m), 3.29-3.18(2H, m), 2.64-2.49(2H, m), 1.91(2H, d), 1.16(6H, d)

MP:214-215°C

Example 147

N-(1-Methylethyl)-3-(methylsulfonyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

4-Fluoro-N-(1-methylethyl)-3-(methylsulfonyl)benzoic acid (J.Med.Chem (1997), 40(13), 2017-2034) (0.45g) was reacted with carbonyldiimidazole (0.37g) and isopropylamine (0.25g) using the method of example 115 step (i) to yield the corresponding amide. Yield 0.50g.

A solution of this amide (0.50g) in 1-methyl-2-pyrrolidinone (10ml) was treated with 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.40g) followed by *N,N*-diisopropylethylamine (0.73g) and the resultant mixture heated at 100°C for 14h. The mixture was then partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. The resultant solid was washed with ethyl acetate (10ml) followed by ethanol (1ml) to yield the desired product as a solid (0.13g).

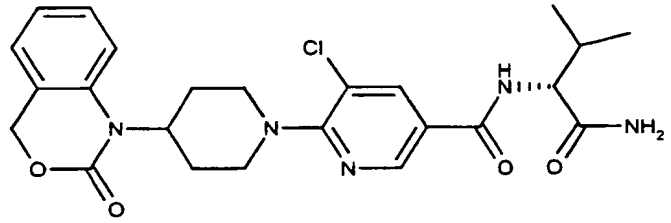
MS: APCI(+ve) 472 (M+1)

1H NMR: δ (DMSO-d6) 8.47(1H, d), 8.38(1H, d), 8.16(1H, d), 7.63(1H, d), 7.42(1H, t), 7.32-7.29(2H, m), 7.13(1H, t), 5.16(2H, s), 4.14-4.05(2H, m), 3.49(3H, s), 3.32-3.29(2H, m), 3.03(2H, t), 2.83-2.76(2H, m), 1.91-1.88(2H, m), 1.17(6H, d)

MP:240-242°C

Example 148

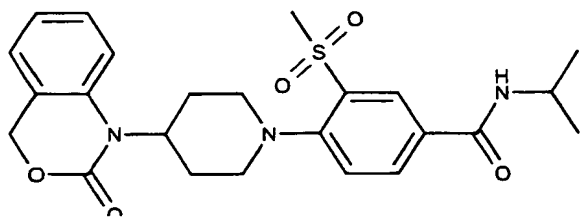
N-[(1R)-1-(Aminocarbonyl)-2-methylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide



(i) 5-Chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxylic acid

The title compound was prepared from 5,6-dichloronicotinic acid (2.2g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (3.0g) using the method of example 115 step (ii). Yield 0.037g

MS: APCI(+ve) 388 (M+1)



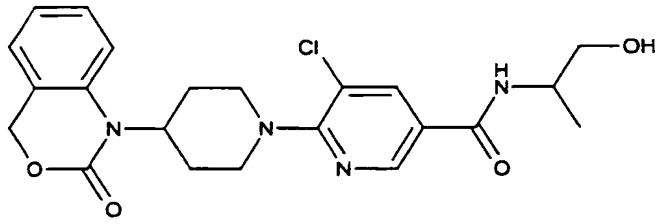
(ii) N-[(1R)-1-(Aminocarbonyl)-2-methylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

The product of step (i) (0.14g) was dissolved in 1-methyl-2-pyrrolidinone (4ml) and to this solution was added carbonyldiimidazole (0.064g) the mixture was stirred at room temperature for 1h and then treated with D-valinamide hydrochloride (0.11g) and *N,N*-diisopropylethylamine (0.10g). After stirring for 18h at room temperature the mixture was partitioned between aqueous sodium bicarbonate and ethyl acetate, the organic layer was washed with water, dried and evaporated under reduced pressure. The resultant solid was washed with ethyl acetate to yield 0.06g of product.

MS: APCI(+ve) 486 (M+1)
1H NMR: δ (DMSO-d6) 8.68(1H, d), 8.31-8.27(2H, m), 7.46(1H, s), 7.42-7.29(3H, m), 7.13(1H, t), 7.06(1H, s), 5.15(2H, s), 4.26(1H, t), 4.19-4.04(3H, m), 3.07(2H, t), 2.72-2.60(2H, m), 2.14-2.07(1H, m), 1.90(2H, d), 0.94-0.91(6H, m)
MP:140-143°C

Example 149

5-Chloro-N-(2-hydroxy-1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

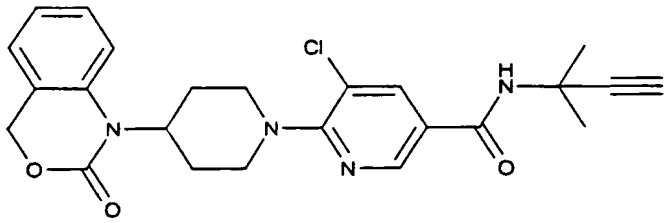


The title compound was prepared from the product of example 148 step (i) (0.14g), carbonyldiimidazole (0.064g) and DL-2-amino-1-propanol (0.05g) using the method of example 115 step (i). Purification was by chromatography eluting with 20% ethyl acetate/isohexane . Yield 0.04g as a solid.

MS: APCI(+ve) 445 (M+1)
1H NMR: δ (DMSO-d6) 8.64(1H, d), 8.20(1H, d), 8.15(1H, d), 7.42-7.29(3H, m), 7.12(1H, t), 5.15(2H, s), 4.72(1H, t), 4.15-3.98(4H, m), 3.48-3.37(2H, m), 3.06(2H, t), 2.73-2.63(2H, m), 1.89(2H, d), 1.13-1.09(3H, m)
MP:125-128°C

Example 150

5-Chloro-N-(1,1-dimethylprop-2-ynyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide



The title compound was prepared from the product of example 148 step (i) (0.14g), carbonyldiimidazole (0.064g) and 1,1-dimethylpropargylamine (0.06g) using the method of example 115 step (i). Purification was by chromatography eluting with ethyl acetate/isohexane (2/3). Yield 0.03g as a solid.

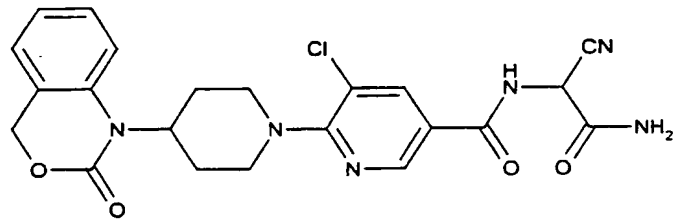
MS: APCI(+ve) 453 (M+1)

1H NMR: δ (DMSO-d6) 8.62(1H, d), 8.29(1H, s), 8.18(1H, d), 7.42-7.29(3H, m), 7.12(1H, t), 5.15(2H, s), 4.19-4.07(3H, m), 3.12(1H, s), 3.07(2H, t), 2.72-2.60(2H, m), 1.90(2H, d), 1.60(6H, s)

MP:135-138°C

Example 151

N-(2-Amino-1-cyano-2-oxoethyl)-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide



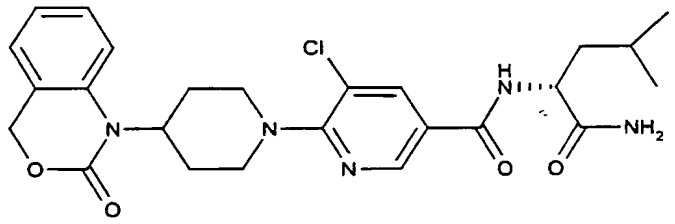
The product of example 148 step (i) (0.14g) was stirred as a suspension in dichloromethane (4ml) and to this mixture was added oxalyl chloride (0.05g) followed by *N,N*-dimethylformamide (0.01g). After stirring for 1h at room temperature the mixture was treated with 2-aminocyanoacetamide (0.14g) 1-methyl-2-pyrrolidinone (3ml) and then *N,N*-diisopropylethylamine (1ml), stirring was then continued for a further 18h at room temperature. The reaction mixture was partitioned between aqueous sodium bicarbonate and ethyl acetate, the organic layer was washed with water, dried and evaporated under

reduced pressure. Purification was by chromatography eluting with 25% ethyl acetate/isohexane . Yield 0.09g as a solid.

MS: APCI(+ve) 469 (M+1)
1H NMR: δ (DMSO-d6) 9.63(1H, d), 8.69(1H, d), 8.25(1H, d), 7.83(1H, s), 7.68(1H, s), 7.40(1H, t), 7.34-7.30(2H, m), 7.13(1H, t), 5.67(1H, d), 5.15(2H, s), 4.17-4.14(3H, m), 3.10(2H, t), 2.69-2.61(2H, m), 1.91(2H, d)
MP:159-162°C

Example 152

N-[(1R)-1-(Aminocarbonyl)-3-methylbutyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

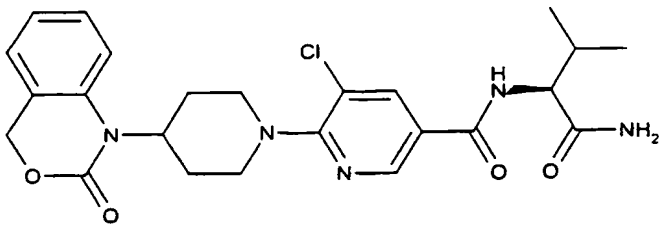


The title compound was prepared from the product of example 148 step (i) (0.15g) and (R)-leucinamide hydrochloride (0.07g) according to the method of example 115, step (i). Yield 0.05g as a solid.

MS: APCI(+ve) 500 (M+1)
1H NMR: δ (DMSO-d6) 8.68(1H, d), 8.45(1H, d), 8.27(1H, d), 7.42-7.29(4H, m), 7.12(1H, t), 6.98(1H, s), 5.15(2H, s), 4.44-4.41(1H, m), 4.15-4.07(3H, m), 3.07(2H, t), 2.68-2.64(2H, m), 1.90(2H, d), 1.70-1.54(3H, m), 0.92-0.86(6H, m)
MP:139-142°C

Example 153

N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

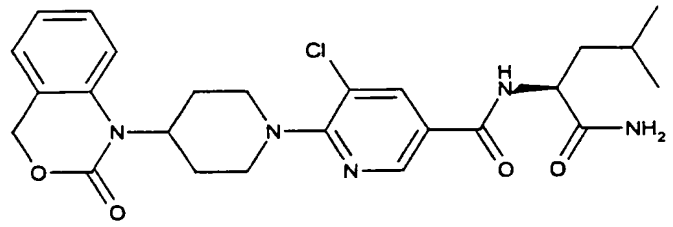


The title compound was prepared from the product of example 148 step (i) (0.15g) and (S)-valinamide hydrochloride (0.08g) according to the method of example 115, step (i). Yield 0.03g as a solid.

MS: APCI(+ve) 486 (M+1)
1H NMR: δ (DMSO-d6) 8.68(1H, t), 8.31-8.28(2H, m), 7.46-7.29(4H, m), 7.13(1H, t), 7.06(1H, s), 5.15(2H, s), 4.24-4.00(4H, m), 3.07(2H, t), 2.73-2.61(2H, m), 2.14-2.05(1H, m), 1.90(2H, d), 0.94(3H, s), 0.92(3H, s)

Example 154

N-[(1S)-1-(Aminocarbonyl)-3-methylbutyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

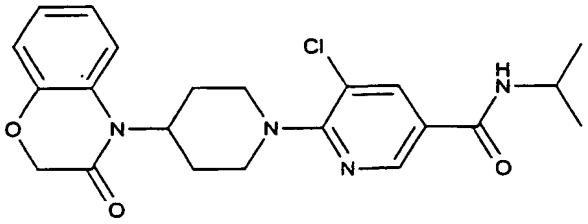


The title compound was prepared from the product of example 148 step (i) (0.15g) and (S)-leucinamide hydrochloride (0.07g) according to the method of example 115, step (i). Yield 0.04g as a solid.

MS: APCI(+ve) 500 (M+1)
1H NMR: δ (DMSO-d6) 8.68(1H, d), 8.45(1H, d), 8.27(1H, d), 7.42-7.29(4H, m), 7.13(1H, t), 6.98(1H, s), 5.15(2H, s), 4.44-4.42(1H, m), 4.15-4.04(3H, m), 3.07(2H, t), 2.68-2.64(2H, m), 1.90(2H, d), 1.66-1.54(3H, m), 0.92-0.86(6H, m)
MP:139-142°C

Example 155

5-Chloro-N-(1-methylethyl)-6-[4-(3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)piperidin-1-yl]pyridine-3-carboxamide

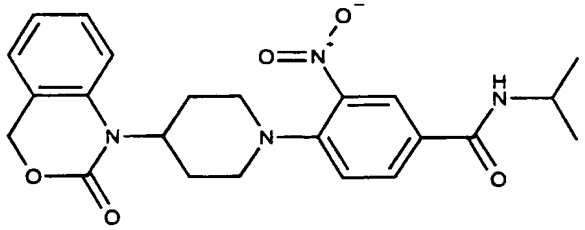


The title compound was prepared from 4-piperidin-4-yl-4H-benzo[1,4]oxazin-3-one hydrochloride (WO 9502405) (0.13g) and the product from example 117 step (i) (0.13g) according to the method of example 115 step (ii). Yield 0.04g as a solid.

MS: APCI(+ve) 429 (M+1)
1H NMR: δ (DMSO-d6) 8.64(1H, d), 8.25(1H, d), 8.18(1H, d), 7.40(1H, d), 7.12-7.03(3H, m), 4.52(2H, s), 4.37-4.32(1H, m), 4.11-4.04(3H, m), 3.03(2H, t), 2.77-2.69(2H, m), 1.82(2H, d), 1.16(6H, d)
MP:85-88°C

Example 156

N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

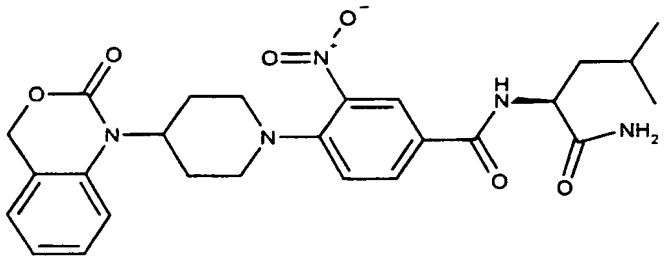


The product from example 8 step (i) (0.05g) was reacted with isopropylamine (0.02ml) using the method of example 115 step (i) in N,N-dimethylformamide (2ml). Purification was by chromatography eluting with (2:1) ethyl acetate/isohexane. Yield 0.035g as a solid.

MS: APCI(+ve) 439(M+1)
1H NMR: δ ($CDCl_3$) 8.17(1H, m), 7.93-7.90(1H, m), 7.38-7.09(5H, m), 5.92-5.90(1H, d), 5.10(2H, s), 4.32-4.16(2H, m), 3.53-3.49(2H, m), 3.17-3.10(2H, m), 2.90-2.80(2H, m), 1.96-1.93(2H, m), 1.28-1.26(6H, d)
MP: 193-195°C

Example 157

N-[(1S)-1-(Aminocarbonyl)-2-methylbutyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



The product from example 8 step (i) (0.05g) was reacted with (S)-leucinamide hydrochloride (0.025g) using the method of example 115 step (i) in N,N-dimethylformamide (2ml). Purification was by chromatography eluting with ethyl acetate. Yield 0.025g as a solid.

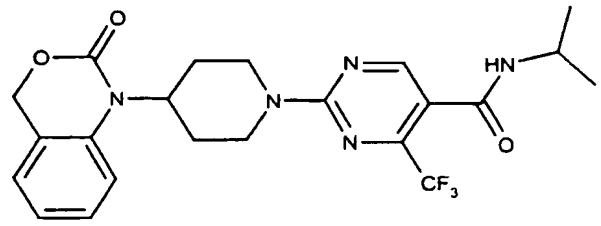
MS: APCI(+ve) 510(M+1)

1H NMR: δ ($CDCl_3$) 8.29-7.09(6H, m), 6.90(1H, d), 6.22(1H, br s), 5.56(1H, br s), 5.10(2H, s), 4.73-4.11(2H, m), 3.50-2.80(6H, m), 1.97-1.70(5H, m), 1.27-1.22(1H, m), 0.99(6H, d)

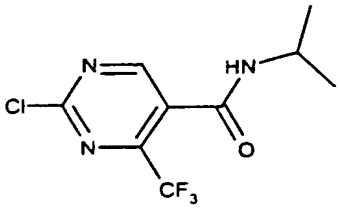
MP: 146-149°C

Example 158

N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)-5-pyrimidine-5-carboxamide.



(i) N-(1-Methylethyl)-2-chloro-4-(trifluoromethyl)pyrimidine-5-carboxamide.



2-Chloro-4-(trifluoromethyl)pyrimidine-5-carbonyl chloride (1.0g) in dry N,N-dimethylformamide (5ml) was treated with isopropylamine (0.4ml) at 0°C. The reaction mixture was stirred at 0°C for 30min, diluted with water, extracted with ethyl acetate, dried, and evaporated under reduced pressure. Purification was by chromatography eluting with 50% ethyl acetate/dichloromethane. Yield 0.74g as a solid.

MS: APCI(+ve) 268(M+1)

(ii) N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl]piperidin-1-yl]-4-(trifluoromethyl)-5-pyrimidine-5-carboxamide.

The title compound was prepared from the product from step (i) (0.092g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.1g) using the method of example 115 step(ii). Purification was by chromatography eluting with (1:3) ethyl acetate/dichloromethane. Yield 0.110g as a solid.

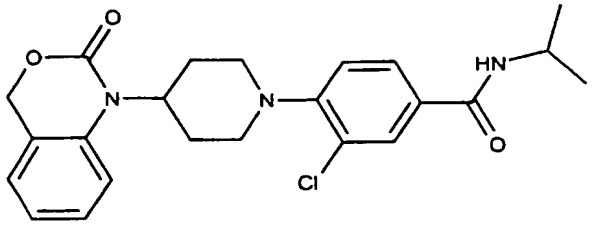
MS: APCI(+ve) 464(M+1)

1H NMR: δ ($CDCl_3$) 8.58(1H, s), 7.38-7.08(4H, m), 5.62-5.60(1H, d), 5.10-5.05(4H, m), 4.29-4.15(2H, m), 3.06-2.62(4H, m), 1.99-1.95(2H, d), 1.25-1.24(6H, d)

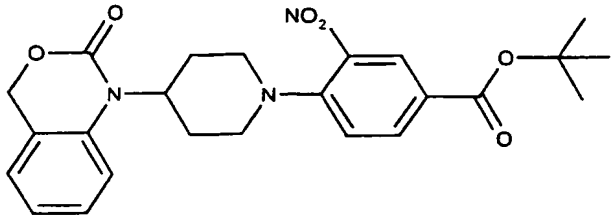
MP: 217-219°C

Example 159

3-Chloro-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



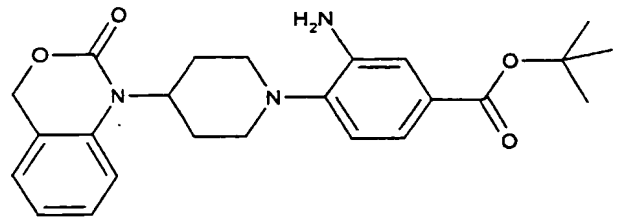
(i) 1,1-Dimethylethyl 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzoate



The product was prepared from 3-nitro-4-chloro-t-butylbenzoate (0.96g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (1.0g) using the method of example 115 step (ii). Purification was by chromatography eluting with 50% ethyl acetate/isohexane. Yield 2.1g as an oil.

MS: APCI(+ve) 454(M+1)

(ii) 3-Amino-1,1-dimethylethyl-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzoate



The product from step (i) (1.9g) was dissolved in glacial acetic acid (20ml) and treated with reduced iron powder (1.9g). The mixture was stirred vigorously for 2h at room temperature. The mixture was filtered through a pad of celite and the filtrate evaporated under reduced pressure. Purification was by chromatography eluting with (1:5) ethyl acetate/ dichloromethane. Yield 0.975g as a solid.

MS: APCI(+ve) 424(M+1)

(iii) 3-Chloro-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

Product from step (ii) (0.39g) was treated with copper(II) chloride (0.148g), isoamylnitrite (0.25ml) in acetonitrile (10ml) and heated to 65°C for 4h. The reaction mixture was

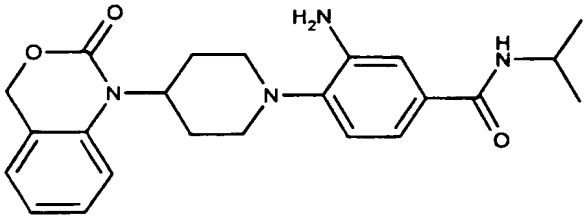
evaporated under reduced pressure to an oil. The oil was treated with trifluoroacetic acid/dichloromethane (1:1) and stirred at room temperature for 2h then evaporated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (5ml), bromo-tris-pyyrolidino-phosphonium hexafluorophosphate (0.116g), isopropylamine (0.054ml) and N,N-diisopropylethylamine (0.06ml) were added and stirred at room temperature for 16h. The mixture was evaporated under reduced pressure. Purification was by chromatography eluting with (1:3) ethyl acetate/dichloromethane. Yield 0.017g as a solid.

MS: APCI(+ve) 428(M+1)

1H NMR: δ ($CDCl_3$) 7.76-7.06(7H, m), 5.82-5.80(1H, d), 5.10(2H, s), 4.31-4.15(2H, m), 3.65-3.62(2H, m), 2.95-2.82(4H, m), 1.98-1.95(2H, d), 1.27-1.25(6H, d).

Example 160

3-Amino-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



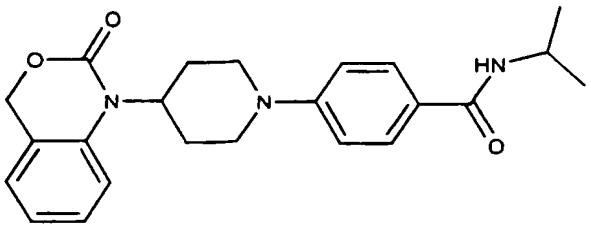
The title compound was prepared from the product of example 156 using the method described in example 159 step (ii). Yield 0.6g as a solid.

MS: APCI(+ve) 409(M+1)

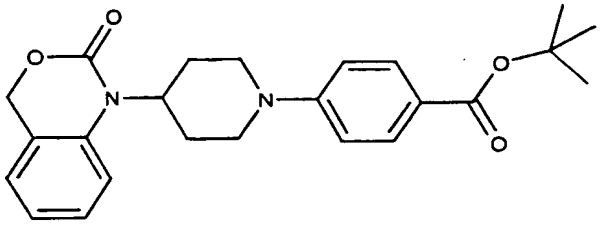
1H NMR: δ (DMSO-d6) 7.89-7.86(1H, d), 7.39-6.91(7H, m), 5.15(2H, s), 4.84-4.82(2H, s), 4.08-3.99(2H, m), 3.23-3.21(2H, m), 2.77-2.67(4H, m), 1.88-1.85(2H, m), 1.19-1.12(6H, d)

Example 161

N-(1-Methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide.



(i) 1,1-Dimethylethyl 4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzoate



A solution of sodium nitrite (0.11g) in water (1ml) was added to a stirred solution of the product from example 159 step (ii) (0.456g) in acetonitrile (10ml) at room temperature. After 1h a solution of iron sulphate (0.3g) in N,N-dimethylformamide (20ml) was added and the mixture stirred for a further 30min. The mixture was partitioned between ethyl acetate and water, the organics dried and evaporated under reduced pressure. Purification was by chromatography eluting with 20% ethyl acetate/isohexane. Yield 0.29g as an oil.

MS: APCI(+ve) 409(M+1)

(ii) N-(1-Methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

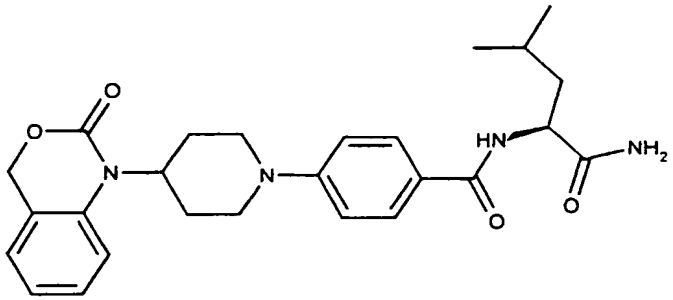
A solution of the product from step (i) (0.29g) in a mixture of trifluoroacetic acid (10ml) and dichloromethane (10ml) was stirred at room temperature for 1h. The solution was evaporated under reduced pressure, the residue dissolved in N,N-dimethylformamide then bromo-tris-pyyrolidino-phosphonium hexafluorophosphate (0.16g), isopropylamine (0.06ml) and N,N-diisopropylethylamine (0.06ml) added. The solution was stirred at room temperature for 16h then evaporated under reduced pressure. Purification was by chromatography eluting with (1:5) ethyl acetate/dichloromethane. Yield 0.01g as a solid.

MS: APCI(+ve) 394(M+1)

1H NMR: δ (DMSO-d6) 7.89-6.95(9H, m), 5.13(2H, s), 4.15-3.97(4H, m), 3.01-2.95(2H, m), 2.59-2.49(2H, m), 1.85-1.82(2H, d), 1.13(6H, d)

Example 162

N-[(1S)-1-(Aminocarbonyl)-3-methylbutyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



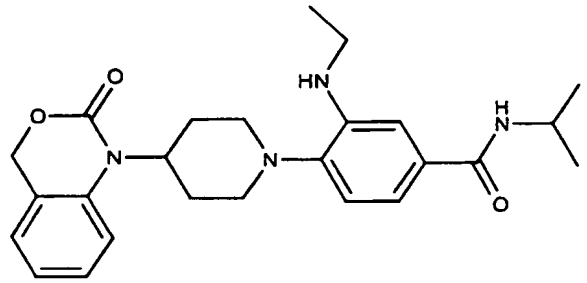
The title compound was prepared from the product of example 161 step (i) (0.06g) and (S)-leucinamide hydrochloride (0.056g) using the method of example 161 step (ii). Purification was by chromatography eluting with (5:1) ethyl acetate/dichloromethane. Yield 0.01g as a solid.

MS: APCI(+ve) 465(M+1)

1H NMR: δ (DMSO-d6) 8.04-6.92(11H, m), 5.13(2H, s), 4.44-3.99(4H, m), 3.03-2.93(2H, m), 2.60-2.49(2H, m), 1.85-1.50(5H, m), 0.88(6H, d)

Example 163

3-(Ethylamino)-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

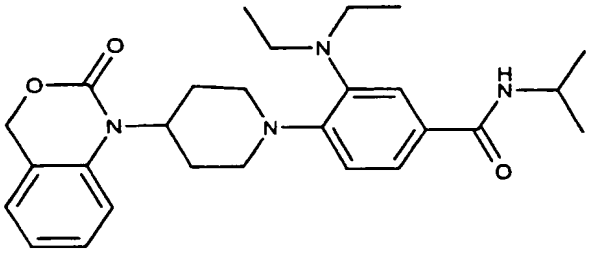


Sodium triacetoxyborohydride (0.1g) was added to a solution of the product from example 160 (0.1g), acetaldehyde (0.015ml), acetic acid (1 drop) in N,N-dimethylformamide (10ml). The reaction mixture was stirred at room temperature for 16h. The mixture was diluted with water, extracted with ethyl acetate, dried, and evaporated under reduced pressure. Yield 0.035g.

MS: APCI(+ve) 437(M+1)
1H NMR: δ (DMSO-d6) 7.96-6.98(8H, m), 5.15(2H, s), 4.73-4.70(1H, t), 4.13-3.99(2H, m), 3.25-3.14(4H, m), 2.81-2.64(4H, m), 1.90-1.88(2H, m), 1.26-1.14(9H, m)

Example 164

3-(Diethylamino)-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

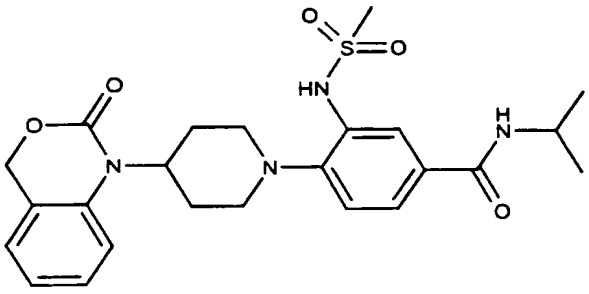


The title compound was obtained from the reaction mixture in example 163. Yield 0.052g.

MS: APCI(+ve) 465(M+1)
1H NMR: δ (DMSO-d6) 7.97-6.90(8H, m), 5.15(2H, s), 4.11-3.99(2H, m), 3.86-3.83(2H, m), 3.31-3.18(4H, m), 2.72-2.63(4H, m), 1.86(2H, m), 1.19-1.14(6H, d), 1.03-0.95(6H, m)

Example 165

N-(1-Methylethyl)-3-[(methylsulfonyl)amino]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide



The title compound was prepared from the product of example 160 (0.1g) and methanesulphonylchloride (0.02ml) in dichloromethane (10ml) at 0°C in the presence of 2,6-lutidine (0.085ml). The reaction mixture was stirred at room temperature for 16h. The mixture was evaporated, dissolved in ethyl acetate, washed with water, dried, and

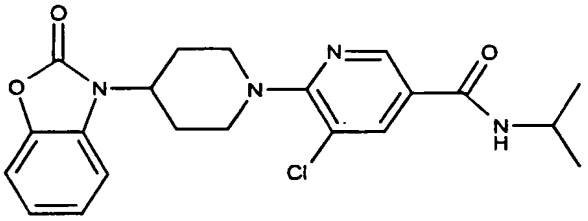
evaporated under reduced pressure. Purification was by chromatography eluting with (3:1) ethyl acetate/isohexane. Yield 0.066g as a solid.

MS: APCI(+ve) 487(M+1)

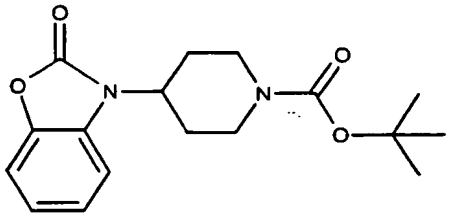
1H NMR: δ (DMSO-d6) 8.63(1H,s), 8.16-8.13(1H, d), 7.76-7.10(7H, m), 5.16(2H, s), 4.14-3.99(2H, m), 3.27-3.23(2H, m), 3.19(3H, s), 2.93-2.70(4H, m), 1.89-1.86(2H, m), 1.17-1.14(6H, d)

Example 166

5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-1,3-benzoxazol-3(2H)-yl)piperidin-1-yl]pyridine-3-carboxamide



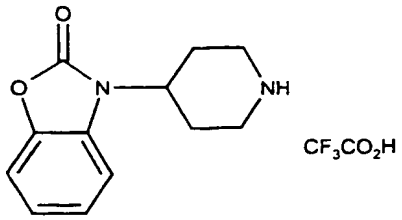
(i) 1,1-Dimethylethyl 4-(2-oxo-1,3-benzoxazol-3(2H)-yl)piperidine-1-carboxylate



2-Benzoxazolinone (1g) was added to a cooled solution of triphenylphoshine (2.13g) and diethylazodicarboxylate (1.28ml) in dry tetrahydrofuran (20ml). After 10min at 0°C, N-(t-butoxy)-4-hydroxypiperidine (1.63g) (Tetrahedron Letters, 1996, 6439-6442) was added portionwise. The reaction mixture was stirred at room temperature for 16h. The solution was diluted with water, extracted with ethyl acetate, dried and evaporated under reduced pressure. Purification was by chromatography eluting with (1:2) diethylether/isohexane. Yield 0.5g as an oil.

MS: APCI(+ve) 219(M+1) -BOC

(ii) 3-Piperidin-4-yl-1,3-benzoxazol-2(3H)-one, trifluoroacetic acid salt



The product from step (i) (0.5g) was stirred at room temperature in (1:1) trifluoroacetic acid/dichloromethane (10ml) for 30min. The reaction mixture was evaporated under reduced pressure to give an oil. Used crude.

MS: APCI(+ve) 219(M+1)

(iii) 5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-1,3-benzoxazol-3(2H)-yl)piperidin-1-yl]pyridine-3-carboxamide

The title compound was prepared from the product of example 117 step(i) (0.53g) and the product from step (ii) by the method described in example 115 step (ii). Purification was by chromatography eluting with 50% ethyl acetate/isohexane. Yield 0.28g as a solid.

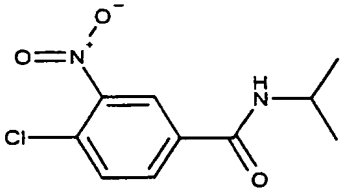
MS: APCI(+ve) 415(M+1)

1H NMR: δ (DMSO-d6) 8.66-7.12(7H, m), 4.44-4.38(1H, m), 4.10-4.05(3H, m), 3.09-3.03(2H, t), 2.45-2.35(2H, m), 1.95-1.92(2H, m), 1.17-1.15(6H, d)

MP: 162-168°C

Examples 167-169

(i) 4-Chloro-N-(1-methylethyl)-3-nitrobenzamide



Isopropylamine (1.28ml) was added dropwise to a stirred solution of 4-chloro-3-nitrobenzoylchloride (3.0g) and triethylamine (2.8ml) in dichloromethane (30ml) at room temperature. After 2h the mixture was partitioned between ethyl acetate and water, the organics dried and evaporated under reduced pressure. Yield 2.87g.

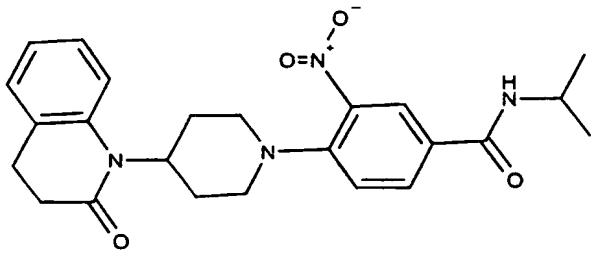
1H NMR: δ (DMSO-d6) 8.58(1H, d), 8.51(1H, d), 8.15(1H, dd), 7.89(1H, d), 4.14-4.06(1H, m), 1.18(6H, d)

(ii) Examples 167-169

A solution of the product from step (i) (1mg), N,N-diisopropylethylamine (3 equiv.), the appropriate amine (1.5 equiv.) in 1-methyl-2-pyrrolidinone (0.16ml) were heated at 65°C for 30h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

Example 167

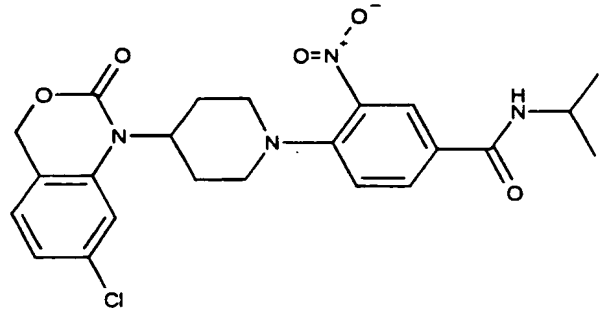
N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]benzamide



MS: APCI(+ve) 436(M+1)

Example 168

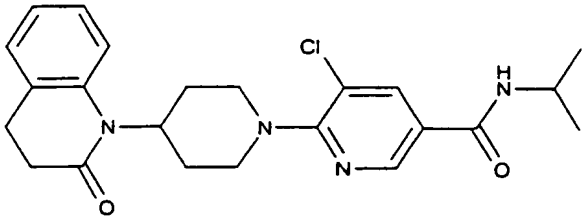
4-[4-(7-Chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1-methylethyl)-3-nitrobenzamide



MS: APCI(+ve) 472(M+1)

Example 169

5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]pyridine-3-carboxamide

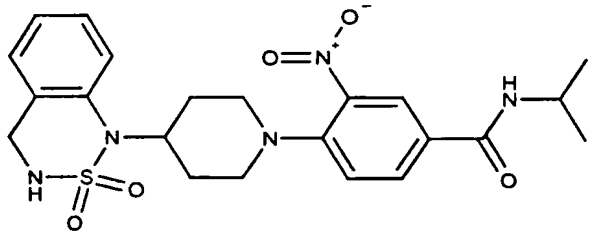


The title compound was prepared from 1-piperidin-4-yl-3,4-dihydro-1H-quinolin-2-one (0.03g) and the product from example 117 step (i) (0.03g) by the method of example 115 step (ii). Purification was by chromatography eluting with 50% ethyl acetate/I-hexane. Yield 0.017g as a white solid.

MS: APCI(+ve) 427 (M+1)
1H NMR: δ (DMSO-d6) 8.49(1H, d), 7.98(1H, d), 7.20(3H, m), 7.02(1H, t), 5.83(1H, d), 4.50(1H, m), 4.20(3H, m), 2.98(2H, t), 2.80(4H, m), 2.60(2H, t) 1.83(2H, m), 1.25(6H, d)

Example 170

4-[4-(2,2-Dioxido-3,4-dihydro-1H-2,1,3-benzothiadiazin-1-yl)piperidin-1-yl]-N-(1-methylethyl)-3-nitrobenzamide



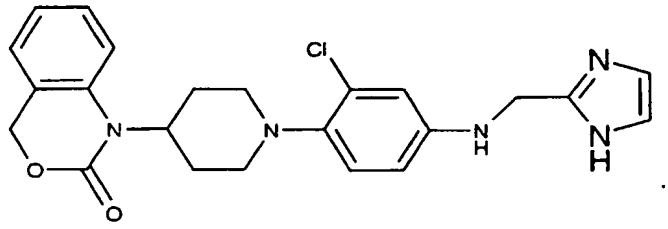
The title compound was prepared from 1-Piperidin-4-yl-3,4-dihydro-1H-benzo[1,2,6]thiadiazine 2,2-dioxide (Chem. Pharm. Bull. (1985), 33(3), 1104-15) (0.05g) and the product from example 167 step (i) (0.05g) by the method of example 115 step (ii). Purification was by chromatography eluting with ethyl acetate. Yield 0.03g as a white solid.

MS: APCI(+ve) 474 (M+1)

1H NMR: δ (DMSO-d6) 8.32 (2H, m), 8.00 (1H, d), 7.72 (1H, t), 7.30 (2H, m), 7.20 (2H, d), 7.10 (1H, t), 4.41 (2H, d), 4.10 (3H, m), 3.40 (1H, m), 3.04 (2H, t), 2.00 (4H, m), 1.15 (6H,d).

Example 171

1-(1-{2-Chloro-4-[(1H-imidazol-2-ylmethyl)amino]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one



The product of example 120 step (ii) (0.25g) was dissolved in 1-methyl-2-pyrrolidinone (6ml) and this solution was treated with 2-imidazolecarboxaldehyde (0.1g) followed by acetic acid (0.13g) and then sodium triacetoxyborohydride (0.37g). the reaction mixture was stirred at room temperature for three days. At the end of this time the mixture was poured in to excess aqueous dilute hydrochloric acid, this solution was allowed to stand for 10 minutes before being basified by addition of excess aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, the organic layer was washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with methanol/chloroform (7/93). Yield 0.05g as a solid.

MS: APCl (=ve) 438 (M+1)

1H NMR: δ (DMSO-d6) 11.84 (1H, s), 7.41 (1H, t), 7.31 – 7.27(2H, m), 7.11(1H, t), 6.97(1H, d), 6.92(2H, s), 6.73(1H, d), 6.57(1H, q), 6.06(1H, t), 5.14(2H, s), 4.19(2H, d), 3.98 – 3.93(1H, m), 3.15(2H, d), 2.78 – 2.63(4H, m) 1.83(2H, d)

MP:222-224°C

Pharmacological Analysis

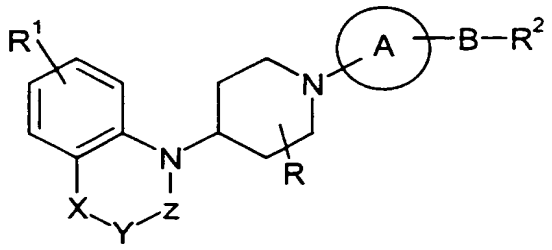
Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the $P2X_7$ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is

observed. The increase in fluorescence can be used as a measure of $P2X_7$ receptor activation and therefore to quantify the effect of a compound on the $P2X_7$ receptor.

In this manner, each of the title compounds was tested for antagonist activity at the $P2X_7$ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 100 µl of test solution comprising 80 µl of a suspension of THP-1 cells (2.5 x 10^6 cells/ml) containing 10^{-4}M ethidium bromide, 10 µl of a high potassium buffer solution containing 10^{-5}M bbATP, and 10 µl of the high potassium buffer solution containing 1 x 10^{-4}M test compound (in 10% v/v DMSO). The plate was covered with a plastic lid and incubated at 37°C for one hour. The plate was then read in a Spectromax Gemini Fluorescent plate reader excitation 525 nm, emission 610 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a $P2X_7$ receptor agonist) and N-(5-methoxy-2-methylphenyl)-tricyclo[3.3.1.$1^{3,7}$]decane-1-acetamide (WO99/29660, a $P2X_7$ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC_{50} figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. The pIC_{50} was then corrected using a modified Cheng Prusoff calculation based on agonist A_{50} (Trends in Pharmacological Sciences (1993), 14(4), 110-2). Each of the compounds of the Examples demonstrated antagonist activity, having a pIC_{50} figure > 5.00.

Claims

1. A compound of formula (I):



(I)

where

A is phenyl or a 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from O, N or S; and optionally substituted by C_{1-6}alkyl, halogen, nitro, amino, alkylamino, CF_3, SO_2Me, $NHSO_2Me$ or cyano;

B is C=O, NH or SO_2;

X is C=O, CH(Me), O or $(CH_2)p$ where p is 0 or 1;

Y is O, CH_2, NH or S;

Z is C=O or SO_2, provided that when Z is C=O, then Y is O, CH_2 or S;

R is hydrogen or C_{1-6}alkyl;

R^1 is hydrogen, halogen;

R^2 is phenyl optionally substituted by CO_2H, CO_2alkyl, $CONH_2$ or R^2 is OH, NHR^3, $NHCH(R^4)(CHR^5)_nR^6$, NH-R^7-R^8, SO_2NHalkyl, NHCOalkyl, $NHSO_2$alkyl, morpholine, NR^9R^{10}, piperazine substituted by phenyl, alkoxyphenyl, pyridyl or fluorophenyl;

n is 0, 1 or 2;

R^3 is hydrogen, a bi- or tricyclic saturated ring system optionally containing a nitrogen atom, piperidinyl, alkylpyrollidine, ethynylcyclohexyl, a 5-membered aromatic ring containing 2 or 3 heteroatoms, C_{4-6} cycloalkyl optionally substituted by alkyl, cyano or hydroxy, or C_{1-8} alkyl optionally containing an oxygen atom in the alkyl chain and being optionally substituted by one or more substituents selected from ethynyl, cyano, fluoro, di-alkylamino, hydroxy, thioalkyl, CO_2R^{11} or $CONH_2$;

R^4 is hydrogen or alkyl optionally substituted by hydroxy or alkoxy;

R^5 is hydrogen or hydroxy;

R^6 is CO_2R^{11}, $NHCO_2R^{12}$, $CONH_2$ or a 5 or 6-membered saturated ring containing an oxygen atom, a 5-membered heterocyclic ring containing one or two heteroatoms selected

from O, N or S, or phenyl optionally substituted by one or more groups selected from alkyl, hydroxy, amino, alkoxy, or nitro;
R^6 is alkyl;
R^7 is a cyclopentane ring;
R^8 is phenyl;
R^9 and R^{10} are independently hydrogen, benzyl, alkenyl, cycloalkyl, alkyl optionally substituted by hydroxy, alkoxy, cyano, dialkylamino, phenyl, pyridyl or CO_2R^{11} or R^9 and R^{10} together form a 5- to 7-membered saturated or partially saturated ring optionally containing a further heteroaton and optionally substituted by one or more groups selected from alkyl (optionally containing an oxygen atom in the chain and optionally substituted by hydroxy), COalkyl, CO_2R^{11}, $COR^{13}R^{14}$, CHO or piperidine,
R^{11} is hydrogen or alkyl;
R^{12} is alkyl; and
R^{13} and R^{14} are independently hydrogen or alkyl,
or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 in which A is phenyl optionally substituted by C_{1-6}alkyl, halogen, nitro, amino, alkylamino, CF_3, SO_2Me, $NHSO_2Me$ or cyano.

3. A compound according to claim 1or 2 in which B is C=O.

4. A compound according to any one of claims 1 to 3 in which X is CH_2, Y is O and Z is C=O.

5. A compound according to any one of claims 1 to 4 in which R is hydrogen.

6. A compound according to any one of claims 1 to 5 in which R^1 is hydrogen.

7. A compound according to any one of claims 1 to 6 in which R^2 is NR^9R^{10} where one of R^9 or R^{10} is hydrogen and the other is alkyl.

8. A compound according to claim 1 which is:
2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoic acid,
1-{1-[2-Nitro-4-(phenylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,

Methyl 2-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoate,
2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzamide,
Methyl 2-({3-nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoate,
2-({3-Nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoic acid,
Methyl 2-({4-[4-(7-chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-3-nitrophenyl}carbonyl)benzoate,

N-(1,1-Dimethylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1R)-2-Hydroxy-1-(phenylmethyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
Methyl 2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propanoate,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(tetrahydrofuran-2-ylmethyl)benzamide,
N-[2-(4-Aminophenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)benzamide,
Ethyl (2S)-3-methyl-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]butanoate,
Methyl 3-hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propanoate,
N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-phenylethyl)benzamide,
N-[(4-Aminophenyl)methyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-thien-2-ylethyl)benzamide,

N-[3-(Dimethylamino)-2,2-dimethylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-{[2,4-Bis(methyloxy)phenyl]methyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Bicyclo[2.2.1]hept-2-yl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(2-Fluoroethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-N-[(3-nitrophenyl)methyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1S,2R)-2-Hydroxy-1-methyl-2-phenylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-{[3,4,5-tris(methyloxy)phenyl]methyl}benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-phenylcyclopropyl)benzamide,
N-[2-Hydroxy-1-(hydroxymethyl)-1-methylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Azabicyclo[2.2.2]oct-3-yl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-piperidin-1-ylethyl)benzamide,
N-(1,3-Dimethylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylhexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(3-Methylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(2-Aminophenyl)methyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[2-Hydroxy-1-(hydroxymethyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[2-(Ethylthio)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,

N-[(1S)-1-(Hydroxymethyl)-2,2-dimethylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(4-Methylcyclohexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-{2-Hydroxy-1-[(methyloxy)methyl]-2-phenylethyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Cyclopropyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
N-(1-Methylpropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
1,1-Dimethylethyl 2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]ethylcarbamate,
N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-{[4-(Methyloxy)phenyl]methyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[2-(1H-Imidazol-4-yl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1S)-1-(Hydroxymethyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-[1-(phenylmethyl)piperidin-4-yl]benzamide,
N-[(1R)-1-(Hydroxymethyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(4-Hydroxybutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-tricyclo[3.3.1.1~3,7~]dec-1-ylbenzamide,
N-[(1S,2S)-2-Hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(2-Hydroxy-1-methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,

N-{2-[(2-Hydroxyethyl)oxy]ethyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[1-(Hydroxymethyl)butyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(2-Amino-2-oxoethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[1-(4-Fluorophenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(3-phenylpropyl)benzamide,
N-[(1S,2R)-2-Hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
Ethyl 3-hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propanoate,
N-[(1R,2S)-2-Hydroxy-1-methyl-2-phenylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
1-{1-[4-(Morpholin-4-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N,N-Dimethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N,N-Bis(2-hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(2-Hydroxyethyl)-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(2-Hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
1-(1-{2-Nitro-4-[(4-phenylpiperazin-1-yl)carbonyl]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N-[(1S,2R)-2-hydroxy-1-methyl-2-phenylethyl]-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Ethyl-N-(2-hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
1-[1-(4-{[4-(4-Fluorophenyl)piperazin-1-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-{1-[4-(Azepan-1-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N,N-Diethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,

N-[2-(Dimethylamino)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
N-Butyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
1-{1-[2-Nitro-4-(piperidin-1-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
Ethyl [({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)(phenylmethyl)amino]acetate,
N-(2-Hydroxyethyl)-N-(1-methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
1-(1-{2-Nitro-4-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-{1-[2-Nitro-4-(pyrrolidin-1-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N-(2-Hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-pentylbenzamide,
N-[2-(Diethylamino)ethyl]-N-ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Ethyl-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
(2S)-1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)pyrrolidine-2-carboxamide,
N-(2-Cyanoethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
1-(1-{4-[(3,5-Dimethylpiperidin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-[1-(4-{[(2R,6S)-2,6-Dimethylmorpholin-4-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-{1-[4-({4-[2-(Methyloxy)phenyl]piperazin-1-yl}carbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-{1-[2-Nitro-4-(thiomorpholin-4-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-(1-{4-[(4-{2-[(2-Hydroxyethyl)oxy]ethyl}piperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,

N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(pyridin-4-ylmethyl)benzamide,
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-prop-2-ynylbenzamide,
1-(1-{4-[(4-Acetylpiperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-[1-(4-{[2-(Hydroxymethyl)piperidin-1-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
4-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazine-1-carbaldehyde,
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
Ethyl 4-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazine-1-carboxylate,
Ethyl 1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidine-4-carboxylate,
1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidine-3-carboxamide,
1-(1-{4-[(4-Methylpiperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-{1-[4-(2,5-Dihydro-1H-pyrrol-1-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N-Ethyl-N-(2-methylprop-2-enyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N,N-Bis(cyanomethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Butyl-N-(cyanomethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N,N-Bis(2-hydroxypropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
1-(1-{4-[(4-Hydroxypiperidin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-(1-{4-[(2,5-Dimethyl-2,5-dihydro-1H-pyrrol-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-propylbenzamide,

N-(2-Amino-2-oxoethyl)-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N,N-Diethyl-1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidine-3-carboxamide,
N-Cyclohexyl-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[2-(Methyloxy)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzenesulfonamide,
1-[1-(4-Amino-2-chlorophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
3-Cyano-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-2-methylpropanamide,
N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}propane-2-sulfonamide,
N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-1-cyanocyclopropanecarboxamide,
(2S)-N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-1-methylpyrrolidine-2-carboxamide,
5-Chloro-N-(1-methylethyl)-6-[4-(4-methyl-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
±-5-Chloro-N-(1-methylethyl)-6-[(cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
±-5-Chloro-N-(1-methylethyl)-6-[(trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1,3,4-thiadiazol-2-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide,

2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1H-pyrazol-3-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(4-Hydroxycyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-[1-(Hydroxymethyl)propyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(3-Hydroxy-2,2-dimethylpropyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(tetrahydrofuran-2-ylmethyl)-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-Cyclobutyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-Cyclopentyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-[2-(1H-Imidazol-4-yl)ethyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(1-Ethynylcyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-[(1R)-1-(Hydroxymethyl)-2-methylpropyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(2-Hydroxy-1,1-dimethylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(1,1-Diethylprop-2-ynyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(2-Hydroxy-1-methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-[1-Methyl-2-(methyloxy)ethyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyrimidine-5-carboxamide,
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-1,3-thiazole-4-carboxamide,
N-(1-Methylethyl)-3-(methylsulfonyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1R)-1-(Aminocarbonyl)-2-methylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,

5-Chloro-N-(2-hydroxy-1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
5-Chloro-N-(1,1-dimethylprop-2-ynyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-(2-Amino-1-cyano-2-oxoethyl)-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-[(1R)-1-(Aminocarbonyl)-3-methylbutyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-[(1S)-1-(Aminocarbonyl)-3-methylbutyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
5-Chloro-N-(1-methylethyl)-6-[4-(3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1S)-1-(Aminocarbonyl)-2-methylbutyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)-5-pyrimidine-5-carboxamide,
3-Chloro-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Amino-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1S)-1-(Aminocarbonyl)-3-methylbutyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-(Ethylamino)-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-(Diethylamino)-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylethyl)-3-[(methylsulfonyl)amino]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-1,3-benzoxazol-3(2H)-yl)piperidin-1-yl]pyridine-3-carboxamide,

N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]benzamide,
4-[4-(7-Chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1-methylethyl)-3-nitrobenzamide,
5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
4-[4-(2,2-Dioxido-3,4-dihydro-1H-2,1,3-benzothiadiazin-1-yl)piperidin-1-yl]-N-(1-methylethyl)-3-nitrobenzamide,
or a pharmaceutically acceptable salt or solvate thereof.

9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8 in combination with a pharmaceutically acceptable diluent, adjuvent or carrier.

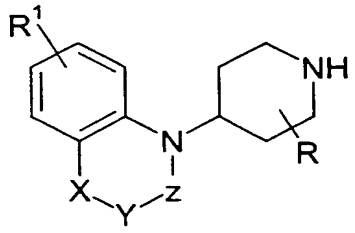
10. A compound according to any one of claims 1 to 8 for use in therapy.

11. A compound according to any one of claims 1 to 8 for use in the treatment of rheumatoid arthritis.

12. Use of a compound according to any one of claims 1 to 8 in the manufacture of a medicament for use in therapy.

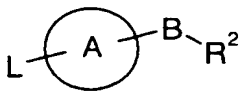
13. A method of effecting immunosuppression which comprises administering to a patient a therapeutically effective amount of a compound according to any one of claims 1 to 8.

14. A process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

where R, R^1, X, Y and Z are as defined in formula (I) or a protected derivative thereof, with a compound of formula (III):



(III)

where B and R^2 are as defined in formula (I) or a protected derivative thereof, and L is a leaving group, and optionally thereafter in any order:

- converting one or more functional groups into further functional groups
- removing any protecting groups
- forming a pharmaceutically acceptable salt or solvate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/02504

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 265/18, C07D 221/22, C07D 495/16, A61K 31/4166, A61K 31/4748, A61P 37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9929686 A1 (ASTRA PHARMACEUTICALS LTD.), 17 June 1999 (17.06.99) --	1-14
A	WO 9613262 A1 (MERCK & CO., INC.), 9 May 1996 (09.05.96), page 12, line 24 - line 25 -- --------	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 2001	20 -04- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Anna Sjölund/EÖ Telephone No. + 46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/02504

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claim 13 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

25/02/01

International application No.
PCT/SE 00/02504

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9929686 A1	17/06/99	AU 1791599 A	28/06/99
		BR 9813378 A	10/10/00
		EP 1037889 A	27/09/00
		NO 20002787 A	01/08/00
		SE 9704546 D	00/00/00
WO 9613262 A1	09/05/96	AU 701127 B	21/01/99
		AU 3967495 A	23/05/96
		CA 2200468 A	09/05/96
		EP 0786997 A	06/08/97
		US 5574044 A	12/11/96
		US 5691323 A	25/11/97